FORMULATION AND EVALUATION OF ORMELOXIFENE FAST DISSOLVING TABLETS

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI-32

In partial fulfillment of the requirement

for the award of degree of

MASTER OF PHARMACY IN PHARMACEUTICS

Submitted By

(Reg. No: 261211307)

DEPARTMENT OF PHARMACEUTICS

COLLEGE OF PHARMACY

MADURAI MEDICAL COLLEGE

MADURAI – 625 020

APRIL – 2014

CERTIFICATE

بسم الله الرحمن الرحيم
In the Name of Allāh, the Most Gracious, the Most Merciful

Prof. Dr. A. ABDUL HASAN SATHALI, M.Pharm., Ph.D,
Principal (i/c),
College of Pharmacy,
Madurai Medical College,
Madurai-625 020, (TN), India.
Email: drabdulhasan@rediffmail.com
Mob: 09443475400

Res: 19, Nallamani Nagar,
Lordu Nagar 12th Street,
K-Pudur,
Madurai – 625007. (TN), India.

CERTIFICATE

This is to certify that the dissertation entitled**, "Formulation and Evaluation of Ormeloxifene Fast Dissolving Tablets"** submitted by **Mr.M.Ramanathan (M. Pharm II year)**, in partial fulfillment of the requirement for the Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by him, under my guidance and supervision in the Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-20 during the academic year 2013 – 2014.

This dissertation is forwarded to the Controller of Examinations, The Tamilnadu Dr. M.G.R. Medical University, Chennai-32.

Place : Madurai

Date :

(Prof. Dr. A. ABDUL HASAN SATHALI)

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

It is my pleasure to express my respectful regards and thanks to ***Dr. B. Santhakumar, M.Sc(F.Sc), M.D(F.M)., PGDMLE., Dip.N.B(F.M)*** *Dean, Madurai Medical College, Madurai for providing all kinds of supportive facilities required to carry out my project work.*

It is my immense pleasure and honour to express my deep sense of gratitude and heartfelt thanks to ***Prof. Dr. A. Abdul Hasan Sathali, M.Pharm., Ph.D.,*** *Principal (i/c)****,*** *College of pharmacy, Madurai Medical College, Madurai, for his excellence in guidance, contribution and encouragement which helped me in the successful completion of each and every stage of my project work.*

I express my heartiest thanks to ***HLL Life care Ltd, Belgaum [KA]*** for giving the pure drug Ormeloxifene as gift sample, ***Jersy Ethical's, Madurai*** (Crospovidone, Croscarmellose sodium) as gift samples and ***Shasun Pharmaceuticals Ltd, Pondicherry*** (PVP K-30) *for providing chemicals to carry out my project work.*

With immense pleasure I record here sincere and hearty thanks to ***teaching and non teaching staff*** *of Department of pharmaceutics for their support and valuable suggestions throughout my work.*

I also thank ***P.S.G. College of Pharmacy, Coimbatore, Karunya University, Coimbatore, and J.S.S College of Pharmacy, Ooty*** *for their help in carrying out the evaluation (IR, X-ray diffraction and DSC) studies.*

I would like to give my sincere thanks to my classmates ***Mr. P. Arjunkumar., Mr. P. Kanniyappan., Mr. A. Manikkavasagan., Mrs. S. Ponnammal Asmi., Mr. C. Pravinkumar., Mr. J. Rajeshkumar., Mr. Sankar Ganesh., Mr. S. Sudhakar*** *for their timely help and co-operation.*

I would like to thank my seniors and juniors for their moral support to carry out my project work.

I also extend my thanks to all the staff members and P.G. Students of Department of Pharmaceutical Chemistry and Pharmacognosy for their Co-operation.

I would like to express my heartfelt thanks to ***my parents, brother and sisters*** *for their moral support to successfully carryout my project work.*

I am extremely thankful to the staff of ***Laser Point*** *for their kind co-operation regarding printing and binding of this project work.*

Place : Madurai

Date :

(RAMANATHAN.M)

CONTENTS

CONTENTS

CHAPTER I

INTRODUCTION

CHAPTER I

INTRODUCTION

Conventional dosage form is very popular because of ease of self administration, compact in nature, easy to manufacture and it can be delivered in accurate dose. Some drugs having poor bioavailability are with poor aqueous solubility and or slow dissolution rate in the biological fluids. Poorly water-soluble compounds with dissolution rate limited and results low oral bioavailability. Solubility is the major challenges in pharmaceutical formulation, all drugs must possess some degree of aqueous solubility, and most drugs should be lipophilic to permeate the biological membranes via passive diffusion. The water solubility of any drug is determined by its potency and its type of formulation. For pharmacological response to be shown the solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation. Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges (Chaudhary V.B and Patel, 2013).

Solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response.

There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increase efficiency and/or reduce side effects for certain drugs. This is true for parenterally, topically and orally administered solutions. The pharmacopoeia lists solubility in terms of dissolve 1g of solute, if exact solubility is not known; the pharmacopoeia provides general terms to describe a given range.

Table a: Expression for approximate solubility definition in USP

Solubility definition	**Parts solvent required for one part of solute**	**Solubility range (mg / ml)**	**Solubility assigned (mg /ml)**
Very soluble	Less than 1	>1000	1000
Freely soluble	From 1-10	100-1000	100
Soluble	From 10-30	33-100	33
Sparingly soluble	From 30-100	10-33	10
Slightly soluble	From 100-1000	1-10	1
Very slightly soluble	From 1000-10,000	0.1-1	0.1
Insoluble or practically insoluble	More than 10,000	<0.1	0.01

General parameters affecting solubility are particle size, shape and surface area physicochemical properties of drugs, and physical forms of drugs, solvents, pH of the medium, temperature and use of surfactants.

Needs of solubility

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response.

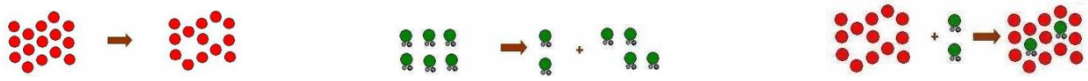
Due to advanced research & development, there are varieties of new drugs & their derivatives are available. But more than 40% of lipophilic drug candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit

potential pharmacodynamic activities. The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action. The basic aim of the further formulation & development section is to make that drug available at proper site of action within optimum dose. (Chaudhary V.B and Patel, 2013)

MECHANISM OF SOLUBILITY

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent.

Step 1 **Step2** **Step 3**



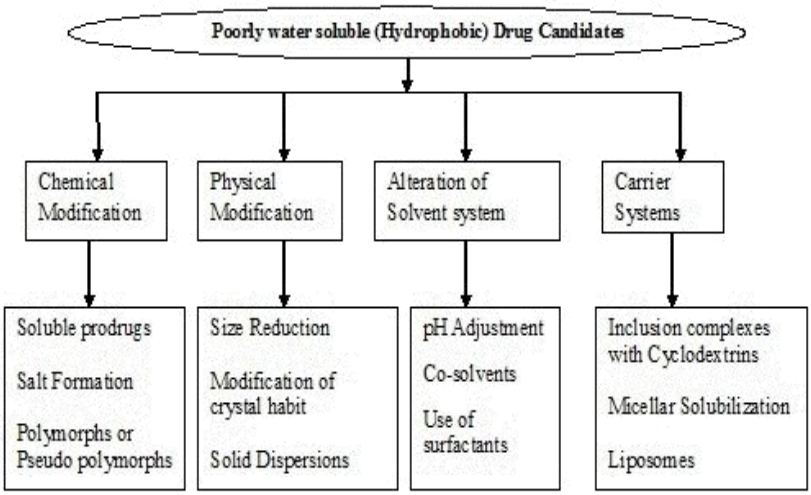
Holes open in the solvent

Molecules of the solid breaks away is integrated into the hole in the solvent

The freed solid molecule

Methods of Solubility Enhancement:

Classical and highly employed approaches to enhance the aqueous solubility and thus the bioavailability of poorly soluble drugs especially, BCS Class II drugs involve the solubilization by application of principles like pH adjustment, cosolvency, microemulsification, selfemulsification,micelles, liposomes and emulsions. Each method is dealing with some merits and demerits. Hence the decision of the method is a crucial step in the formulation process. (Daisy Sharma et al, 2009)



Salt formation:

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Approximately 300 new chemical entities approved by the FDA during the 12 years from1995 to 2006 for marketing, 120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion. Several reviews have outlined general strategies and considerations for salt selection. For the salt formation drug should have ionizable groups that will assist salt formation. The criteria used to select counter ion is as follows:

- There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
- Counter ion should decrease crystal lattice forces.
- It should be FDA approved or should have enough toxicological data to support the
- Selection of the counter ion.

This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules.

Polymeric Alteration:

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability.

Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

Particle Size Reduction:

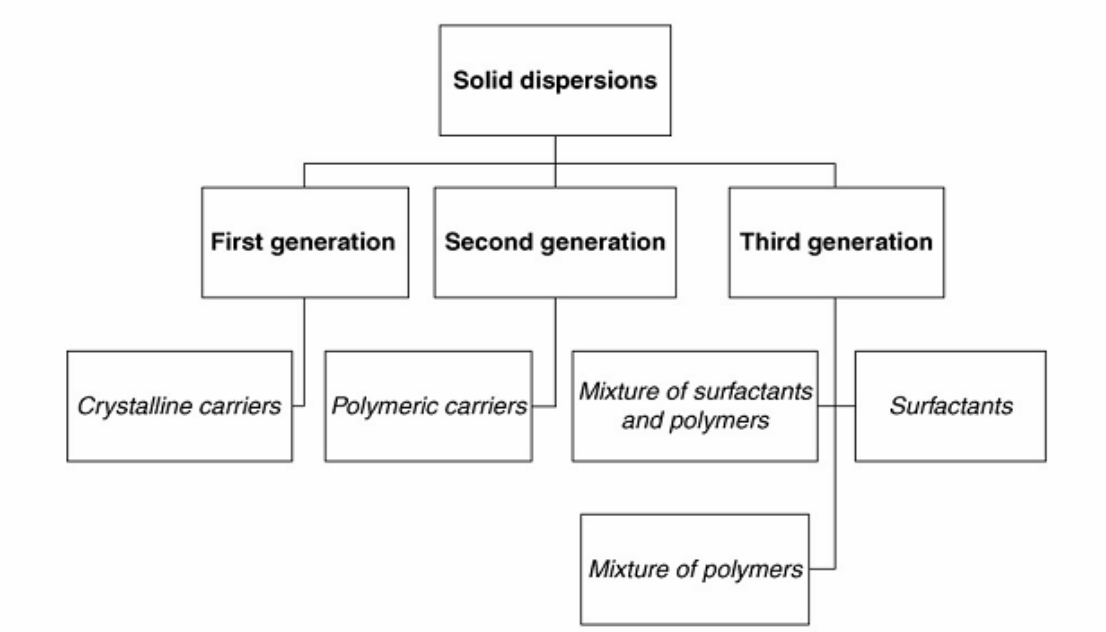
Micronization or nanonization is one of the most potential approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to sub-micron level. Particle size is a critical parameter which should be strictly controlled during the preformulation studies of any formulation. Although the reduction in the particle size is a successful way to enhance the solubility, if uncontrolled and un-optimized, it can lead to re crystallization and re-aggregation of drug on storage. Hence a thorough study on particle size and physical stability should be done. Size reduction to submicron range is not possible by the conventional milling techniques. Patented engineering processes have come up based on the principles of pearl milling high-pressure homogenization, solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS).

SOLID DISPERSIONS

Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method.

CLASSIFICATION

I. BASED ON CARRIERS USED:



a) First generation

First generation solid dispersions were prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and did not release the drug as quickly as amorphous ones.

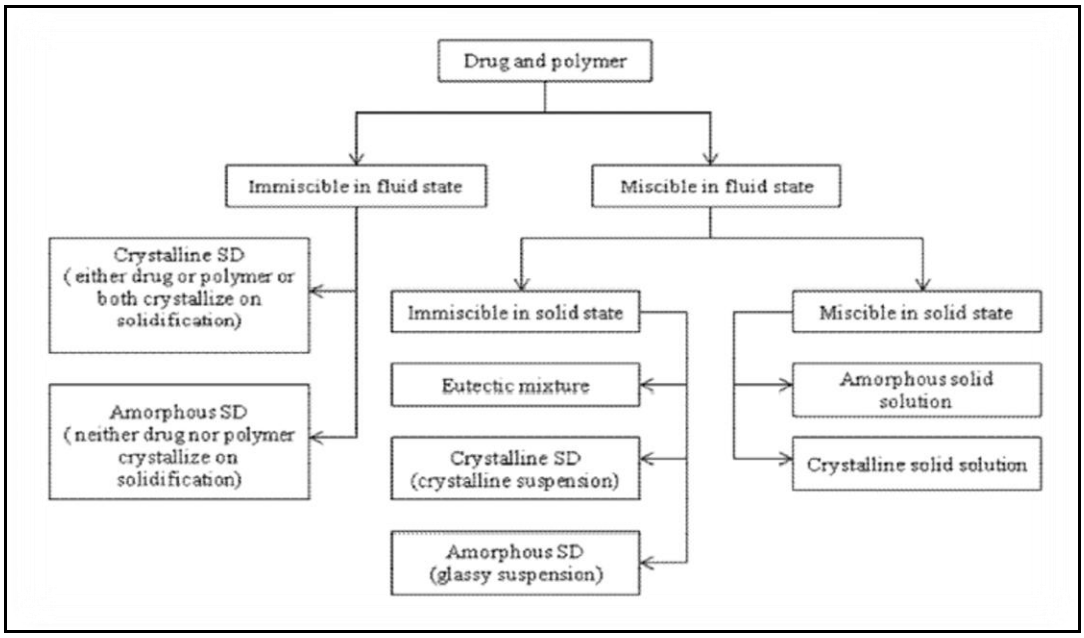
b) Second generation

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates as well as natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropoylcellulose or starch derivates like cyclodextrins.

c) Third generation

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.

II. THE BASIS OF SOLID STATE STRUCTURE (Bhawana Kapoor *et al.*, 2012)



1) Drug and polymer exhibiting immiscibility in fluid state

If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixtures and any enhancement in dissolution performance may be owing to modification in morphology of drug and/or polymer due to physical transformation solid to liquid state and back), intimate drug–polymer mixing, and/or enhanced surface area.

Formation of crystalline or amorphous solid dispersions can be biased by the rate of solidification of mixture and the rate of crystallization of drug and/or polymer.

2) Drug and polymer exhibiting miscibility in fluid state

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion.

a) Eutectic Mixtures

Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug (A) and a carrier (B) are co-melted at their eutectic composition defined by point 'e', as shown schematically in the figure below, the melting point of the mixture is lower than the melting point of either drug or carrier alone. At the eutectic composition (e), both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug.

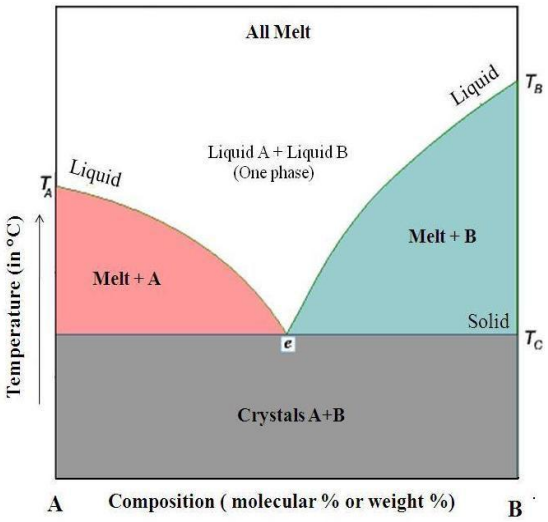


FIGURE: (a) Phase diagram of a eutectic mixture (Bhawana Kapoor *et al.*, 2012)

b) Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies.

c) Amorphous Solid Dispersion

If the drug–polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a "solidified-liquid" state. These types of dispersions have the risk of potential for conversion to a more stable and less soluble crystalline form.

f) Solid Solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. These solid solutions may be either of amorphous or crystalline type. In amorphous solid solutions as the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Amorphous solid solutions have improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility. Crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. According to extent of miscibility of the two components, solid solutions are continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are immiscible at intermediate composition, but miscible at extremes of composition are referred to as discontinuous solid solutions.

According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional and interstitial. In the substitutional solid

solution, the solute molecule substitutes for the solvent molecule in the crystal lattice. Molecular size of the two components should not differ by more than 15%. An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice. For this to occur, the solute molecule diameter should be less than 0.59 than that of solvent molecule. Therefore, the volume of the solute molecule(s) should be less than 20% of the solvent molecule(s). Examples include solid solutions of digitoxin, methyltestosterone, predinsolone acetate and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit faster rate of dissolution.

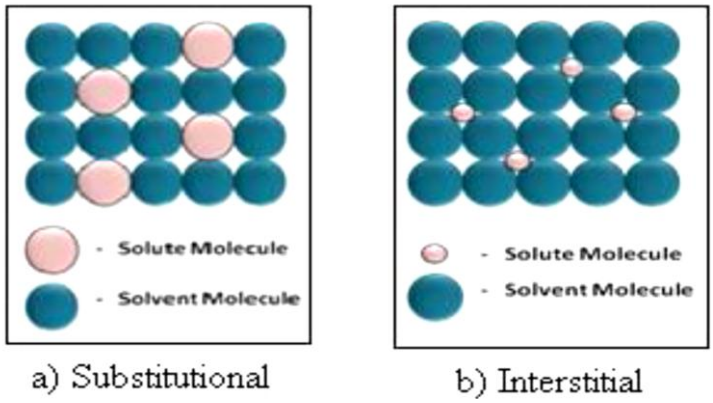


FIGURE-(b): Schematic representation of sub stituitional solid solution and interstitial solid solution

DIFFERENT METHODS OF PREPARATION OF SOLID DISPERSION

Several approaches have been attempted for the preparation of solid dispersion, to improve the solubility and dissolution characteristics of poorly water-soluble drugs which include (Ahuja Nitika, et al., 2012)

1) Spray drying
2) Fusion method
3) Solvent evaporation
4) Hot-melt extrusion

5) Particle size reduction
6) Supercritical fluid (SCF) processes.
7) Kneading
8) Inclusion Complexes
9) Direct Capsule filling
10) Electrostatic Spinning Method
11) Surface-active Carriers
12) Melt agglomeration

(1) Spray drying

In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is evaporated at 400C under reduced pressure by using vacuum evaporator, obtained mass is dried in a desiccators over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent. The product is crushed, pulverized & sieved through a suitable mesh number sieve.

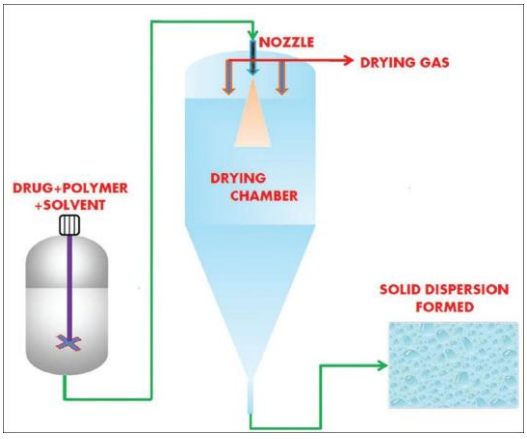


Figure (c): Schematic representation of spray drying technique (Ahuja Nitika *et al.*, 2012)

(2) Fusion method

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath.

(3) Solvent Removal Process

In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, obtained mass is dried in a desiccator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve.

(4) Hot-Melt Extrusion

The extruder consists of a hoper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die. The effect of screw revolution speed and water content on the preparation of SD(s) should be investigated, since these parameters have profound impact on the quality of SD(s). In addition, high screw speed –high feed rate processes in comparison with low screw speed–low feed rate processes caused an increase in extrudate radius and porosity and decrease in mechanical strength and drug release rate from the matrix attributed to the expansion promoted under certain extrusion conditions.

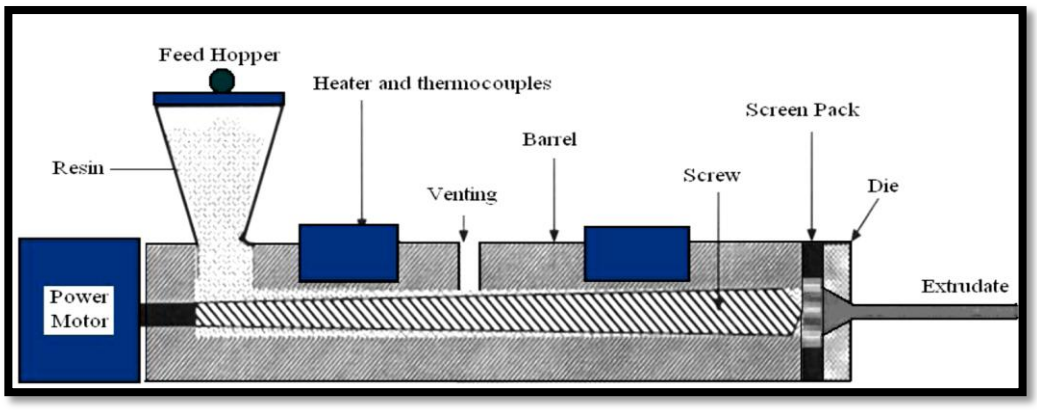


FIGURE-(d): Single screw melt extruder (Bhawana Kapoor *et al.*, 2012)

(5) Particle size reduction

By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound (Ahuja Nitika *et al.*, 2012).

(6) Supercritical Fluid (SCF) Processes

A SCF is a substance that exists above its critical point, which is defined by the conditions of temperature and pressure at which liquid and gaseous states of a substance coexist. When a liquid is heated, its density continues to decrease, while the density of vapor being formed continues to increase. At the critical point, densities of liquid and gas are equal and there is no phase boundary, as shown in Figure (e). Above the critical point that is, in the supercritical region, the fluid possesses the penetrating power typical of a gas and the solvent power typical of a liquid.

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an antisolvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are

immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of

organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO_2 of most pharmaceutical compounds is very low (<0.01 wt-%) and decreases with increasing polarity (Bhawana Kapoor et al., 2012)

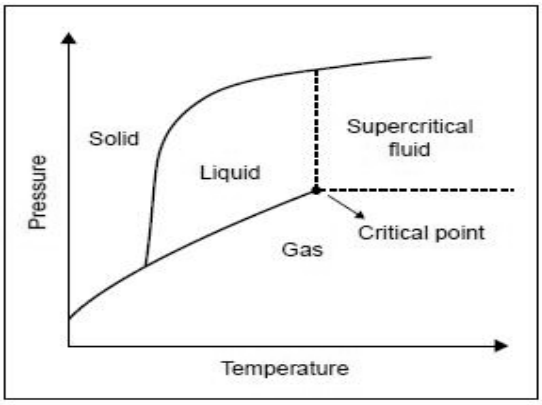


Fig (e): Supercritical region

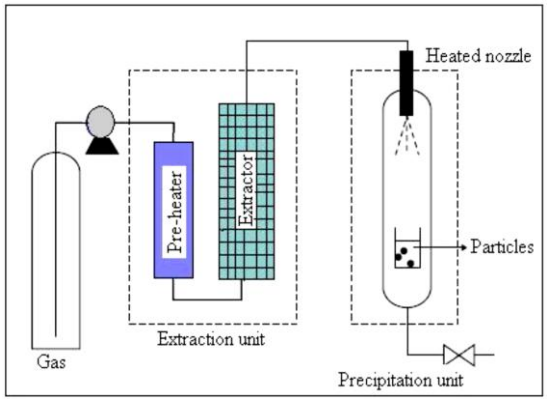


Fig 7: Schematic of the RESS apparatus used in compound supercritical fluid technology

(g) Kneading

In this method a mixture of drug and carrier is wetted with methanol and kneaded thoroughly for 30 minutes in a glass mortar. The paste is dried under vacuum for 24 hours. Dried powder is passed through sieve no. 60 and stored in a dessicator (Prabhakar Shirse et al., 2012)

(8) Inclusion Complexes

The improvement in solubilisation ability within these water soluble polymer/drug included CD aggregates requires less cyclodextrin to solubilise the same amount of drug, reducing the volume constraints present for non-aggregated CDs and increasing the range of delivery technologies available. Drug-CD complexes are commonly formed through either supersaturating a CD solution with drug and mildly agitating the solution for an extended period of time, or adding a mass of drug to a CD and solvent slurry and 'kneading' to produce a paste which is then dried and sieved.

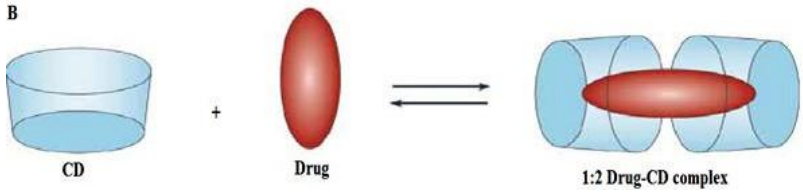


Figure (f): Cyclodextrin [polymer]-drug complex

APPLICATIONS OF SOLID DISPERSIONS

To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

1. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.
2. To reduce side effect of certain drugs.
3. Masking of unpleasant taste and smell of drugs.
4. Improvement of drug release from ointments, creams and gels.
5. To avoid undesirable incompatibilities.
6. To obtain a homogeneous distribution of a small amount of drug in solid state.
7. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
8. To formulate a fast release primary dose in a sustained released dosage form.

9. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
10. To reduce pre-systemic inactivation of drugs like morphine and progesterone (Arunachalam *et al.*, 2010).

Direct Capsule Filling-

The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. It was not until much later that the potential application of the technique for solid dispersions was fully realized. Laboratory scale semiautomatic equipment and large scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. For example, the filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule filling machine (Zanasi Co, Bologna, Italy)

Electrostatic Spinning Method-

Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the

electrostatic force. The columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest. This technique can be utilized for the preparation of solid dispersions in future.

Surface-active Carriers-

A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. The surface active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions.

Melt agglomeration process

This technique has been used to prepare solid dispersion where the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder (melt in procedure) or by spraying a dispersion of drug in molten binder on the heated excipients (spray on procedure) by using a high shear mixer. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersions by melt agglomeration. It has been investigated that the spray on

procedure with PEG-3000, Poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition, the melt in procedure also results in homogeneous distribution of drugs in agglomerate. (Bhawana Kapoor et al., 2012).

CHAPTER II

FAST DISSOLVING TABLET – A REVIEW

CHAPTER II

FAST DISSOLVING TABLET-REVIEW

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules;

Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug dissolves into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European pharmacopoeia adopted the term “Orodispersible tablet” as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes.

The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is

subjected to first pass metabolism is reduced as compared to standard tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities (Debjit Bhowmik et al., 2009).

Criteria for Fast dissolving Drug Delivery System:

The tablets should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

Salient Features of Fast Dissolving Drug Delivery System:

- Ease of Administration to the patient who can not swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.

- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

- ❖ Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Benefits of fast dissolving tablets

- ❖ Administered without water, anywhere, any time.
- ❖ Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.
- ❖ Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- ❖ An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- ❖ Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Limitations of Mouth Dissolving Tablets

- ➢ The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- ➢ The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly (Debjit Bhowmik et al., 2009)

TECHNIQUES FOR PREPARING FAST DISOLVING TABLETS:

Many techniques have been reported for the formulation of fast dissolving tablets or orodispersible tablets.

1) Freeze drying / lyophilization
2) Tablet Moulding
3) Spray drying
4) Sublimation
5) Direct compression
6) Mass extrusion

Freeze-Drying or Lyophilization

This technique creates an amorphous porous structure that can dissolve rapidly. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine.

Tablet Molding:

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution.

The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

Spray Drying:

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation:

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by

sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents.

Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1:

Saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2:

Saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

Mass-Extrusion:

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking. (Shailesh Sharma, 2008 & Debjit Bhownmik et al., 2009)

EVALUATION OF FAST DISSOLVING TABLETS:

Preformulation Studies:

- Bulk density
- Tapped density
- Angle of repose
- Carr's index or % Compressibility
- Hausner ratio
- Precompression drug content

Post compression studies:

- Weight variation
- Hardness
- Thickness
- Friability
- Wetting time

- Water absorbtion ratio
- Disntegration test
- Invitro dreg release study
- Solubility test
- Stability studies

CHAPTER III

LITERATURE REVIEW

CHAPTER III

LITERATURE REVIEW

Shaimaa N.Abd Alhammid *et al.*, 2013, studied for formulation and evaluation of Rosuvastatin Orodispersible tablet prepared by using a super disintagrant croscarmillose, sodium starch glycolate and crospovidone to enhance the disintegration and dissolution. Many trails were made to prepare an ODT by direct compression and wet granulation method. Overall result showed that crospovidone was the best super disintegrant on showing the shortest disintegration time and manitol was the best diluents in preparing Rosuvastatin Orodispersible tablet. Formulation containing 15 % crospovidone showed best drug release profile.

Mohan kumar *et al.*, 2013, reviewed solubility enhancement techniques. The various technological strategies reported in this literature, like solid dispersion, polymorphisim, complexation, hydrotrophy, co-solvency, pH adjustment, use of salt form, use of precipitation inhibitors, eutectic mixture, miceller solubilisation, super critical fluid technique, micronization, use of surfactants and newer techniques like Nano technology approaches, self emulsifying drug delivery system, solid lipid nano particle, and cryogenic technology. The present review described various novel techniques for enhancing drug solubility and improving bioavailability.

Payal H.Patil *et al.*, 2013, studied on solubility enhancement of Roloxifene using inclusion complex and cogrinding method. The study work was to enhance the solubility and dissolution of water insoluble drug Rolaxifene Hcl. The first approach drug was kneaded with hydroxyl propyl betacyclodextrin (HPBCD) and in the second one was co-grinded with modified guar gum (MGG). The result showed the inclusion complex method has produced better results as compare to other methods and thus was found to be more effective than co grinding method.

Abhilash M *et al.*, 2013, formulated and evaluated of solid dispersion of Melitracen. In this study the drug has low solubility which results poor bioavailability. In the present study was an attempt to increase solubility by solid dispersion technique. The best formulation was compressed in to fast dissolving tablets using crospovidone as a super disintagrant by direct compression technique. The highest invitro drug release was observed in Betacyclodextrin solid dispersion ratio of 1:3 drug and carrier.

Thakur Anil Kumar *et al.*, 2013, studied on various techniques enhancing bioavailability of poorly water soluble drugs. This article described various methods to enhance solubility like encapsulation with cyclodextrin, nano technology approaches and hydrotrophy. The described techniques alone or in combination can be used to enhance the solubility of drugs. Selection of solubility enhancement method depends upon drug characteristic like solubility, chemical nature, melting point, absorption site, physical nature and pharmacokinetic behavior.

Debjit *et al.*, 2013, reviewed recent trends of polymer usage in the formulation of orodispersible tablets. The present study comprised the various kinds of disintagrants and superdisintagrants, which were used in the formulations to provide the safer and effective drug delivery with patient's compliance.

Chaudhary V.B and Pate J.K., 2012, developed a formulation of inclusion complex to enhance the solubility of poor water soluble drugs. complexation with cyclodextrin by different methods like physical mixing, melting , kneading, spray drying , co precipitation has been reported to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Ravi S Wanare and Ravikant S Murkute., 2012, developed a formulation and evaluation of Azithromycin fast dissolving tablet by wet granulation method. In this study fast dissolving tablet formulated with various super disintegrants such as

croscarmellose sodium, sodium starch glycolate and crospovidone. In all the formulation water was used as a binding agent. Amongst all formulation formula F_7 containing sodium starch glycolate- 30mg produced least disintegrating time of 21.4 seconds and faster dissolution.

Anas Bahnassi *et al.*, 2012, formulated aceclofenac fast dissolving tablet. The poor hydrophilicity of the drug results in variable dissolution rate and poor bio availability. The aceclofenac orodispersible tablet was prepared by using various types of disintegrants. Formulation containing plasdone xl 100 30 mg showed comparatively better drug release and disintegration time profile.

Prabhakar Shires et *al*., 2012, formulated and evaluated cyclodextrin inclusion complex of glimipride tablet. The rationale of this study was to enhance the solubility & dissolution of the drug by prepared its complex with ßcd and hp-ß-cd. In the present study was an attempt to formulate and characterize inclusion complexes of glimepiride with ß-cd and hp-ß-cd. The inclusion complexes were prepared by three different methods viz. Physical, kneading and coprecipitation method. The inclusion complex containing glimipride: ß-cd and hp-ß-cd was further formulated into tablets by direct compression technique using super-disintegrants like crospovidone and microcrystalline cellulose. The prepared tablets were characterized using FT IR , DSC study and other evaluations.

Amit Modi *et al.*, 2012, developed a formulation and evaluation of diclofenac sodium fast dissolving tablets using different super disintegrant like sodium starch glycolate, croscarmellose sodium and crosspovidone [poly plasdone XL] by direct compression method. The tablet were evaluated for weight variation, hardness, friability, disintegration time wetting time, invitro dissolution studies and drug content. It was concluded that the batch which was prepared by using combination of crospovidone

and sodium starch glycolate as a super disintagrant shows excellent short disintegration time, enhanced dissolution rate, and hence leas to improve efficacy and bioavailability of drug.

Dhaval Shah *et al.*, 2012, studied on development and characterization of mouth dissolving tablet of zolmitriptan tablets were prepared by direct compression method employing super disintegrants such as kyron T-314, crospovidone, croscarmellose sodium and sodium starch glycolate. Prepared zolmitripan mouth dissolving tablet containing kyron T-314 exhibited shortest disintegration time of 35 seconds. To further decrease the disintegration time, a sublimation technique was also used along with super disintegrants for the preparation of MDT.

Parul Saini et al., 2012, reviewed natural polymers used in fast dissolving tablets. The aim of the article was to study the natural polymers used in FDT formulation . Natural polymers like magnifera indica gum, hibiscus rososinenses mucilage, dehydrated banana powder, orange peel pectin,locustnbean gum, which improved the properties of tablet and also used as a binder and diluents. Natural polymers are obtained easily from the natural origin and they are cost effective, nontoxic biodegradable, eco friendly devoid of any side effect renewable and also provide nutrinal supplements.

Abdul Hasan Sathali A. and Selvaraj V., 2012, studied the enhancement of solubility and dissolution rate of racecadotril. Solid dispersion of racecadotril was prepared with carriers of poly vinyl pyrrolidone k 30, poly ethylene glycol 6000 and poloxamer 188 by using kneading, melting, solvent evaporation, freeze drying and physical mixture. The interaction between drug and carrier was evaluated by Fourister Transform infra red (FT IR) and Differential scanning colorimetry studies, powder x-ray diffraction (PXRD) studies were also carried out the crystallinity of solid

dispersion. The results indicated drug and carrier (PVP K- 30) 1:3 ratio by kneading method produced best release.

Karthikeyan *et al.,* 2012, developed a formulation of diclofenac tablets for rapid pain relief. The object of the project was to get fast pain relief. Fast dissolving tablet was prepared by direct compression method using indion 214, indion 234, indion 244 and crosscarmellose as super disintegrant , micro crystalline cellulose was used as a diluents and manitol as a sweating agent. The formulation containing indion 244 showed quick disintegration time of 29.66 seconds. Indion 244 was found to have high superdisintegrant property.

Devandra Revanal Rane *et al.,* 2012, studied on formulation and evaluation of fast dissolving tablet of albendazole. The main object of the study was to formulate fast dissolving and improving bioavailability of the drug. Fast dissolving tablet prepared by direct compression method using super disintegrant crospovidone, croscarmellose sodium in different concentration. Among all the formulation containing 5%$^{w}/_{w}$ super disintagrant crospovidone and 20% $^{w}/_{w}$ MCC was considered to be best formulation which release was up to 99.09% in 40 seconds.

Hyma .P *et al.,* 2012 , studied on improvement of solubility and dissolution rate of pioglitazone by solid dispersion technique. Pioglitazone is a poor water solubility drugs. The main objective of the study was to develop solid dispersion with polymers like polyethylene glycol – 4000, PEG – 6000, in the ratio 1:1, 1:2, 1:3, 1:4 and 1:5 by solvent evaporation technique. The solid dispersion with PEG – 6000 [1:5] ratio showed best drug release where compare to solid dispersion with PEG- 4000 and other polymers.

Ashish Kumargarg *et al,* 2012, reviewed mouth dissolving tablets significants, Ideal properties of MDT, challenges in formulation, various formulation methods, list of super disintegrants and evaluation methods.

Claudia Yanez *et al.,* 2012, developed a cyclodextrin inclusion complex to improve physicochemical properties of herbicide bentazon. The inclusion complex prepared by two methods, kneading and freeze drying. Formulation characterization was investigated by different analytical techniques including Fourier transform infra red spectroscopy (FT IR), Diffential thermal analysis (DTA), X- ray diffractometry (XRD) and differential pulse voltametry (DPV). The result indicated inclusion complex by cyclodexrin shows improved physiochemical properties compare to free bentazon.

Anjan K.Mahapatra *et al.*,2012, described an overview of theoretical definitions and technical approaches was broadly covered (technologies and hydrophilic carriers used). Further part of manuscript is committed to the formulation, analytical methods for characterization of samples, dissolution or release kinetics and model fittings.

Imran Shekh *et al.,* 2011, developed a preparation and characterization of betacyclodextrin with aspirin inclusion complex. The aim of the work was to study the influence of betacyclodextrin on asprin. The best formulation was betacyclodextrin and asprin solid dispersion, 1:2 drug and carrier ratios showed best drug release of 96.05%.

Saravanakumar *et al,* 2011, reviewed fast dissolving tablets background, trends and future. This article described ideal properties of mouth dissolving tablets, mechanism of disintagrtion, method of preparing fast dissolving tablets, preformulation studies, evaluation studies and various patented fast dissolving tablet technologies..

Ashish.P *et al.,* 2011, reviewed on formulation of mouth dissolving tablet. The aim of this article was to review the progress of the evolving technologies and super disintegrating agents in the formulation, manufacturing and evaluation of tablets. This article was also discussed the evaluation methodologies for orally disintegrating tablets. In the present review described the formulation techniques and different evaluation techniques are discussed.

Anupama singh et al., 2011, studied on evaluation and enhancement of solubility of paracetamol by solid dispersion technique using different polymer concentration. The aim of the study was to prepare characterize and compare solid dispersion of paracetamol using PEG – 4000 and polyvinyl pyrolidone used for enhancing the dissolution rate of drug. The solid dispersion was prepared by physical mix method and kneading method at 1:1, 1:2 and 2:1, ratio of drug and polymer, based on the drug release pattern the kneading method showed more drug release as compare to physical mixture.

Nagendra Rao R et al., 2011, designed a solubility and dissolution enhancement of Cefixime using natural polymer by solid dispersion.. In the present work was an attempt to increase the solubility of cefixime by preparing solid dispersion using natural polymers (i.e.) guar gum. Various techniques used for preparing solid dispersion by Physical mixture, kneading and solvent evaporation method using different drug polymer ratio. Thus prepared solid dispersion was evaluated for percentage of yield, drug content, saturation solubility and invitro dissolution studies. Among the various methods comparison kneading method produced best drug release profile.

Shobhit Kumar *et al.,* 2011, studied on aceclofenac dissolution rate enhancement by solid dispersion technique. The aim of the study was to prepare and characterizes

solid dispersion of aceclofenac employing a mixed excipient system, used composed of lactose, corn starch as a carrier. The solid dispersion were prepared by physical mixture method and solvent wetting methods using 1:1 ratio of drug to mixed excipient system. Best formulation selection was based on the drug release pattern, the solvent wetting method showed more invitro drug release as compare to physical mixture method.

Seitia Anupama *et al.,* 2011, studied design, optimization, preparation and evaluation of albendazole using factorial design. The objective of the study was to enhance the solubility and dissolution rate of albendazole, a poor water soluble anthelmintic drug, by preparation of solid dispersions. The dispersion granules were prepared using a hot melting technique which involved preparation of a homogenous dispersion of albendazole in gelucire 44/14 and PEG 8000. A two-factor, four-level (4*2) statistical design was implemented to quantitate the influence of gelucire 44/14 and PEG 8000 on the dissolution profile, where gelucire 44/14 and PEG 8000 were chosen as independent variables, while T10 min (cumulative drug release in 10 minutes) and T60 min (cumulative drug release in 60 minutes) were chosen as dependent variables. The solid dispersions were characterized for their in-vitro dissolution rate. The optimized formulation was further characterized by DSC, XRD and SEM analysis. In conclusion the statistical model enabled us to understand the effects of formulation variables on the dispersion

Yogesh S Thorat *et al.,* 2011, reviewed a study on solubility enhancement technique- of conventional and novel approaches. This article described bioavailability issues; it can be due to insufficient solubility, thus leads to low permeability. Pharmaceutically the bioavailability approaches to correct with chemical approaches, which are also

time consuming process, each technique has several merits and demerits. In this review study was an attempt of comparing the conventional and novel techniques.

Jagadevappa patil *et al.*, 2010, study has performed with the intension of finding the effect simvastatin preparation with beta cyclodextrin and hydroxyl propyl beta cyclodextrin inclusion complex. The method of preparation of complex was simple physical mixture, kneading method, and spray drying method. They done following evaluations drug content, Aqueous solubility and invitro drug release studies. Conclusion exhibits Spray drying method were shown better solubility then other methods.

Tomar V *et al.*, 2010, developed a formulation for Enhancement of solubility of Acyclovir by solid dispersion and inclusion complex method. The solubility of Acyclovir was found to be more with inclusion complex as compare to solid dispersion technique. The result showed that hydroxy propyl betacyclodextin inclusion complex could possibly improved the dissolution characteristics of acyclovir (1:5 ratio) shows better release then other formulations.

Sawarikar P.P *et al.*, 2010, the investigation aim was to develop and evaluate inclusion complex of isoxuprine hydrochloride with betacyclodextrin using kneading and co precipitation method. The resultant product was used to prepare Fast dissolving tablet by using super disintegrants like Sodium starch glycolate, croscarmelose (ac-di-sol) and crospovidone by direct compression method. The formulation containing Ac di sol 5% showed complete release of drug within 4 minutes.

Suhas M.Kakade et al., 2010, developed a formulation and evaluation of mouth dissolving tablets of losartan potassium. Mouth dissolving tablets prepared by direct compression method using super disintegrants like Polyplasdone xl 10, croscamellose

sodium and explotab in different concentration and evaluated for the pre compression parameters such as bulk density, compressibility, angle of repose etc. among all the formulation 5% $^{w}/_{w}$ super disintegrant polyplasdone XL-10 was consider to be best formulation which release up to 99.26% in 12 minutes.

Jeevana Jyothi.B and Suneela G., 2010, formulated a fast dissolving tablet of glibenclamide using crospovidone by its kneading method. The object of the work was to develop fast dissolving tablet of glibenclamide using crospovidone in ratio of 1:0.5, 1:1, and 1:1.5. The tablet were prepared by using kneading mixture by wet granulation method. The mixture prepared in the ratio of drug and crospovidone as 1:1.5 by kneading method shows best release.

Arun Prasad K *et al.*, 2010, formulated and evaluated of solid dispersion of Terbinafine hydrochloride. The study was aimed to formulate solid dispersion of terbinafine hydrochloride tablet by using carriers polyethylene glycol 6000 [by melting method] polyvinyl pyrrolidone K 30 [by solvent method] in the drug carrier ratio 1:1, 1:2, and 1:3. The prepared solid dispersion was characterized for drug content, thermal studies, FT IR, DSC, studies and dissolution. The solid dispersion showed better drug release profile which is chosen to formulate into a tablet dosage form.

Appa Rao et al., 2010, developed a formulation and evaluation of aceclofenac Solid dispersion for dissolution rate enhancement. Solid dispersion of Aceclofenac were prepared by using lactose, manitol and urea to increase its aqueous solubility. The prepared solid dispersion was subjected for % of practical yield, drug content and IR studies. The maximum yield was found to be 97.92% in [Aceclofenac : urea -7:3 ratio]. The drug release profile formulation 9:1 ratio [Aceclofenac : Polymer Lactose]which showed best release.

Vineet Bhardwaj et al., 2010, The objective of the present study was to prepare the mouth dissolving tablet of Amlodipine using different superdisintegrants by sublimation method. Different concentrations 2%, 4% and 6% of superdisintegrants such as Ac-Di-Sol, sodium starch glycolate, Kollidon-CL were used respectively. Camphor was used as a sublimating agent. Tablets are prepared by direct compression method and mannitol is used as bulking agent. The compressed tablets are dried for 5 hours to allow sublimation of camphor to increase the porosity of the fast dissolving tablets to improve the dissolution. The tablets were evaluated for hardness, friability, weight variation, wetting time, thickness, water absorption ratio, disintegrating time, uniformity of content and in-vitro drug release. Amongst all formulations, 6% Ac-Di-Sol containing formulation showed least disintegrating time of 11sec.and faster dissolution.

Kothawade et., al, 2010 investigation was an attempt made to improve the solubility and dissolution rate of a poorly soluble drug, telmisartan solid dispersions were prepared using Polyvinyl pyrrolidone (PVP), Polyethylene glycol-1500 (PEG-1500) and Polyethylene glycol-4000(PEG-4000) to increase its aqueous solubility. Telmisartan solid dispersions were prepared in 1:1, 1:2 and 1:4 ratios of the drug to polymer ratio (by weight) using solvent evaporation method. The formulations were characterized for solubility parameters, drug content studies, drug release studies and drug-polymer interactions by using FTIR spectrum. Formulation containing 1:2 ratio of drug: PEG-4000 showed the best release with a cumulative release of 99.49% as compared to 35.82 % for the pure drug.

Mohamed Gulzar Ahmed and et al., 2010, study was aimed to improving the dissolution of poorly water-soluble drug, aceclofenac. The solid dispersions were prepared in different proportions using hydrophilic carriers like Urea and Mannitol.

The dissolution rate studies were performed in both simulated gastric fluid and simulated intestinal fluid. It is observed that the dissolution was affected by the acidity of the medium. Solid dispersions gave faster dissolution rate when compared to corresponding physical mixture and pure drug, invivo absorption and anti-inflammatory activity studies of solid dispersions also confirmed the above results.

Deepthi Mathew et al., 2009, developed a Nimusulide – Betacyclodextrin complex in oral and topical dosage forms. The object of the project was to enhance the aqueous solubility of nimusulide by using aqueous solubility carriers. Nimusulide – Betacyclodextrin solid complex are formulate by co precipitation method. The invitro drug release profile study showed dissolution of Nimusulide has improved, by complexation with BCD. The prepared complexes ware suitable for oral and topical formulations.

Shukla Vikesh et al., 2009, studied the Influence of Betacyclodextrin complex on ketoprofen release from matrix formulation. The objective of this study was to improve dissolution profile and the bioavailability of the ketoprofen. The invitro release demonstrated that matrix tablet containing the ketoprofen with betacyclodextrin solid complex displayed faster drug release compare with physical mixture and free drug. Formulation prepared by co- precipitation and kneaded ketoprofen with betacyclodextrin. The result indicated inclusion complex has faster dissolution rates.

Debjit Bhowmik et al., 2009, presented a study on overview on fast dissolving tablets. The article which describes the various methods to prepare fast dissolving techniques such as Freeze drying, Tablet molding, Spray drying, Sublimation, Direct compression, Mass extrusion and important patented technologies, evaluation methods, and brief about preformulation monitoring studies.

Daist Sharma et al., 2009, studied on solubility enhancement and reviews eminent role in poorly soluble drugs. The present review was devoted to production of solid dispersion with various carriers used and the advantageous properties of solid dispersion.

Jain C.P and Smnaruka P, developed valsartan fast dissolving tablet formulation and evaluation. Fast dissolving tablet was prepared by direct compression method using super disintagrant crospovidone, croscarmelose sodium and sodium starch glycolate . the result showed increase drug release by increase the concentration of super disintagrants and was found to be highest with formulation containing crospovidone.

Brahmeshwar Mishra et al., 2009, this study was attempt to describe a detailed review on technological advances made so for in the area of evaluation of mouth dissolving tablets with respect to special characteristics of these unique dosage forms. In the absence of any available standardized method the author recommendation on critical issues in the field may be considered.

Mohini and et al, 2009, The objective of this research was to formulate fast dissolving tablet of amlodipine besylate for rapid action. Sublimation method was adapted to prepare the tablets by using a 2 full factorial design. FT-IR and D.T.A studies revealed that there was no physico-chemical interaction between amlodipine besylate and other excipients. All formulations are evaluated for pre-compression and post-compression parameters. The results indicate that the optimized tablet formulation provides a short DT of 8 sec with sufficient crushing strength and acceptable friability.

Shallesh Sharma et al., 2008, formulated **a** new generation – Fast dissolving tablets. The study describes the importance of fast dissolving formulation and various

methods used to prepare fast dissolving tablets. This article describes the details on preformulation, evaluation and ingredient profile and its properties.

Kamal Dua et al., 2007, investigated study for norfloxacin solubility with presence of acidic solublizing additives. The study is aimed for improving the solubility of drugs. Norfloxacin has incorporating with solubilizing additives such a ascorbic acid and citric acid in to betacyclodeextrin complexes. It exhibits a higher solubility at p^H below4 and above 8. In the present work betacyclodextrin were prepare along with solubilizing additives such as citric acid and ascorbic acid in proportion. The results has showed an enhanced dissolution rate both p^H 1.2 and p^H 7.4 media

CHAPTER IV

AIM OF THE WORK

CHAPTER IV

AIM OF THE WORK

Solubility of a drug is an important property that mainly influences the extent of oral bioavailability. The new chemical entities about 40% are poorly water-soluble. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to solubility concerns. It is therefore becoming increasingly more important that, the methods for overcoming solubility limitations may be identified and applied commercially such that, the potential therapeutic benefits of these active molecules can be realized.

Ormeloxifene is a selective estrogen receptor modulator drug, which is widely used for the management of dysfunctional uterine bleeding, contraceptive and emergency contraceptive. It is chemically 3, 4 trans 2, 2 dimethyl 3, phenyl-4(p) beta pyrrolidinoethoxy phenyl 7 methoxy chroman hydrochloride.

One of the major problems with this drug is its very low solubility in biological fluids, which results into poor bioavailability after oral administration. It belongs to class II drug according to biopharmaceutical classification system (BCS), that is, low solubility and high permeability. It would be advantageous to increase the solubility of such molecule. Further it is important to enhance aqueous solubility and dissolution rate, which may lead to enhancement of bioavailability from its oral solid dosage form.

In the formulation point of view conventional dosage forms (Tablets and capsules) take higher disintegration time, so that the pharmacological action is delayed by 30-45 minutes from its administration. To overcome this problem tablets

that can rapidly disintegrate or dissolve (within one minute) in oral cavity have attracted a great deal of attention.

In this study comprise of two steps, the first step is to improve the aqueous solubility of ormeloxifene hydrochloride by solid dispersion technique, using polymers like betacyclodextrin and polyethylene glycol 6000 by solvent evaporation, melting, co-precipitation and kneading methods.

The second step is compression of fast dissolving tablet, by using the yield of best solid dispersion formulation with various super disintagrants like crospovidone, sodium starch glycolate and crosscarmellose sodium by direct compression technique. The best formulation selection is on the basis of drug release pattern, disintegration time, water absorption ratio, and wetting time.

CHAPTER V

PLAN OF WORK

CHAPTER V

PLAN OF WORK

I. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ-max for Ormeloxifene in Distilled water and phosphate buffer pH 6.8.

b) Calibration of Ormeloxifene in distilled water

c) Calibration of Ormeloxifene in phosphate buffer pH 6.8.

II. COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS

1) Fourier Transform Infra Red Spectroscopic (FT-IR) studies

III. FORMULATION AND EVALUATION OF SOLID DISPERSIONS

a. Formulation and evaluation of solid dispersion by different techniques.

b. Determination of percentage of yield for all formulations

c. Determination of drug content of all formulation

d. Invitro dissolution studies of solid dispersion.

e. Selection of best formulation based on the invitro drug release studies.

IV.EVALUATION OF SELECTED FORMULATION

a) Powder X-Ray Diffraction (PXRD) studies

b) Fourier Transform Infrared spectroscopic study of best formulation.

c) Solubility study of solid dispersion.

d) Differential Scanning Calorimetric (DSC) Studies

V. PREFORMULATION STUDY FOR FAST DISSOLVING TABLETS

VI. FORMULATION OF ORMELOXIFENEFAST DISSOLVING TABLET

By direct compression method, using different superdisintagrants.

VII. POST COMPRESSION EVALUATION OF FAST DISSOLVING TABLETS.

VIII. BEST FORMULATION SELECTION

IX. STABILITY STUDIES

CHAPTER VI

MATERIALS AND EQUIPMENTS

CHAPTER VI

MATERIALS AND EQUIPMENTS

Material	Supplier
Ormeloxifene	Gift sample from HLL Life care Ltd, Belgaum [KA]
Beta cyclodextrin	Hi Media Laboratories Pvt. Ltd, Mumbai
PEG – 6000	S.D Fine chemicals Ltd, Mumbai
Sodium starch glycolate	High Purity Laboratory Chemicals Pvt. Ltd, Mumbai.
Crospovidone	Gift sample from Jersy Ethical's, Madurai
Croscarmellose sodium	Gift sample from Jersy Ethical's, Madurai
Micro crystalline cellulose	High Purity Laboratory Chemicals Pvt. Ltd, Mumbai.
PVP K-30	Shasun Pharmaceuticals Ltd, Pondicherry
Mannitol	Nice chemicals Pvt. Ltd, Cochin
Magnesium Stearate	High Purity Laboratory Chemicals Pvt. Ltd, Mumbai.
Talc	Universal scientific suppliers, Madurai
Methanol	Universal scientific suppliers, Madurai

Details of Equipments

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A&D Company, Japan.
Single punch tablet compression machine	Cadmach Machinery Co. Pvt, Ahmadabad.
UV Visible spectrophotometer	Shimazdu UV-1700, Japan.
Digital tablet dissolution test apparatus	Lab India Disso apparatus 2000, India.
Friability test apparatus	Indian Equipment corporation, Mumbai.
Tablet hardness tester	Praveen Enterprises, Bangalore.
Vernier caliper	Linker, Mumbai.
Disintegration test apparatus	Rolex, India.
Fourier transform infrared spectroscopy	Shimadzu, Japan.
Differential scanning colorimeter	DSC Q200 V24.4 Instrument , USA.
Powder X-ray diffractometer	XD, Shimadzu, Japan.
Magnetic stirrer	M.C. Dalal, Chennai.
Mechanical shaker	Secor, India.
Environmental Chamber	Inlab Equipments (P) Ltd, Chennai.

CHAPTER VII

DRUG PROFILE

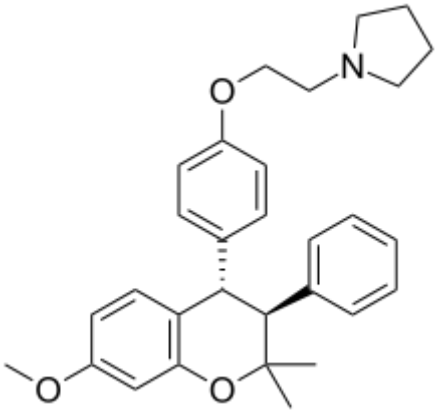
CHAPTER VII

DRUG PROFILE

Ormeloxifen HCl

Synonym : Centchroman

Structure :



Formula : $C_{30}H_{35}NO_3$

Molecular weight : 457.604 g/mol

Systematic iupac name : 1-[2-[4-[(3*S*,4*R*)-7-methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl]phenoxy]ethyl] pyrrolidine

Appearance : Off- white powder

Solubility : Soluble in chloroform and methanol Sparinglly soluble in ethanol (95 %) Very slightly soluble in water

Melting point : 212° c to 218° c

Log P **:** 7.41

Half life **:** 4 Hours

Route of administration **:** Oral

Dose **:**

Contraception:

30 mg twice a week for the 1st 12 weeks then 1 tablet (30 mg) once a week from 13th weeks onwards. Take 1st tablet on the 1st day of menstrual cycle. Follow dose irrespective of menstrual periods.

DUB:

60 mg twice a week for the 1st 12 weeks and then

60mg once a week for up to next 12 weeks.

Dosage form:

Tablets --- 30 mg and 60 mg

(Jawahar Lal, Elsevier, 2009)

Pharmacodynamics:

Ormeloxifene is a SERM, or selective estrogen receptor modulator. In some parts of the body, its action is estrogenic (e.g., bones), in other parts of the body, its action is anti-estrogenic (e.g., uterus, breasts.) It causes an asynchrony in the menstrual cycle between ovulation and the development of the uterine lining. It did not affect ovulation in the majority of women, while causing the lining of the uterus to build more slowly.

It speeds the transport of any fertilized egg through the fallopian tubes more quickly than is normal. Presumably, this combination of effects creates an environment such that if fertilization occurs, implantation will not be possible.

Pharmacokinetics:

Ormeloxifene is administered by the oral route, is well absorbed from the intestinal tract and Peak plasma levels are attained in about 4 hour and terminal half life of the drug is 170 hours. Protein binding is 90 % Safety in, lactation and renal / hepatic insufficiency is inadequate, which requires care in the usage.

Absorption:

centchroman is rapidly absorbed, with a maximum serum concentration (Cmax) varying from 117 to129 ng/mL and it observed 4 h after drug ingestion.

Distribution:

Centchroman is widely distributed within the body due to its high lipid solubility in healthy women. The apparent volume of distribution is higher than the total body fluid and the mean residence time (MRT) is 128 days. Moreover, nursing females showed comparable Vd/F to that of non nursing females treated orally. Therefore, breastfeeding does not appear to affect the distribution of this drug. Centchroman binds strongly to serum albumin in healthy subjects (~90%) in the individual serum samples with inter subject variability in protein binding of centchroman. The binding increases with an increase in total protein content.

Metabolism:

centchroman is metabolized by rat liver homogenate in vitro to biologically active (7-desmethyl chroman, 2-desmethyl chroman and 2-monomethyl chroman) and inactive metabolites, with active metabolites contributing to estrogen agonistic and anti-implantation activities, while inactive metabolites accounting for its gradual metabolic disposition . A marked increase in activity of hepatic microsomal aniline hydroxylase, aminopyrine N-demethylase, cytochrome P450 and cytochrome b, indicating rapid disposal of the compound from the body, has also been observed in

adult female rhesus monkeys treated with 25 mg/kg dose of centchroman 8 h before autopsy.

Elimination:

Studies regarding the metabolism of centchroman in humans are scarce. In serum and milk, the demethylated metabolite (7-desmethyl centchroman) has been reported after the oral administration of centchroman to healthy volunteers

Drug–drug interactions:

Co-administration of tetracycline yielded significantly higher C (35%) and a shorter time to reach Cmax(t) for centchroman (42%) than those obtained in the control group of females. Inclusion of lactic acid bacillus spores in the regimen resulted in similar effects with increase in Cmax (47%)

Adverse effect:

Delayed menses

(Jawahar Lal, Elsevier, 2009)

CHAPTER VIII

EXCIPIENTS PROFILE

CHAPTER VIII

EXCIPIENT PROFILE

Betacyclodextrins

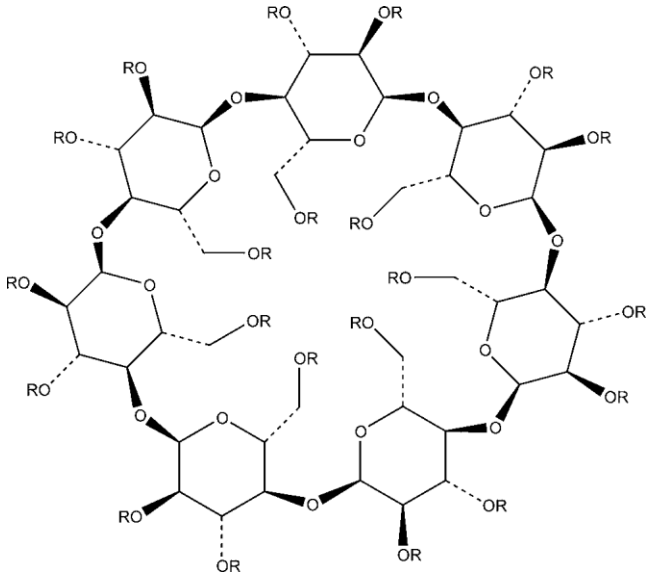
Synonyms:

- b-Cyclodextrin beta-cycloamylose
- Beta-dextrin
- Betadexum

Empirical Formula **:** $C_{42}H_70_{35}$

Molecular Weight **:** 1135

Structural Formula:



Functional Category:

Solubilizing agent; stabilizing agent.

Pharmacopeial specifications

Compressibility	**:**	**0.523 g/cm**
Density (tapped)	**:**	**0.754 g/cm**

Solubility : Soluble 1 in 200 parts of propylene glycol, 1in50 of water at 208C, 1 in 20 at 508C; practically insoluble in acetone, and ethanol (95%).

Specific rotation : D25= þ162.08;

Surface tension (at 258C) n : 71 mN/m (71 dynes/cm);

Stability and Storage Conditions:

β-Cyclodextrin is stable in the solid state if protected from high humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

Method of Manufacture:

Betacyclodextrin is produced by the action of the enzyme cyclodextrin glucosyltransferase upon starch or a starch hydrolysate. An organic solvent is used to direct the reaction that produces betacyclodextrin, and to prevent the growth of microorganisms during the enzymatic reaction. The insoluble complex of betacyclodextrin and organic solvent is separated from the non cyclic starch, and the organic solvent is removed in vacuum so that less than 1 ppm of solvent remains in the betacyclodextrin. The betacyclodextrin is then carbon treated and crystallized from water, dried, and collected.

Safety:

- nontoxic and nonirritant
- cyclodextrins are approved for use in food products and orally administered pharmaceuticals in a number of countries.
- Cyclodextrins are not irritant to the skin and eyes, or upon inhalation.
- There is also no evidence to suggest that cyclodextrins are mutagenic or teratogenic.

Handling Precautions: should be handled in a well-ventilated environment.

CROSPOVIDONE

SYNONYMS:

- Crosslinked povidone
- Kollidon
- Polyplasdone
- Polyvinylpolypyrrolidone
- 1-vinyl-2-pyrrolidinone homopolymer

CHEMICAL NAME:

1-Ethenyl-2-pyrrolidinone homopolymer

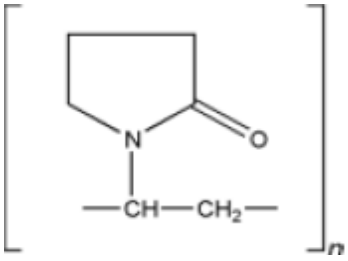
EMPIRICAL FORMULA:

$(C_6H_9NO)_n$

MOLECULAR WEIGHT:

>1 000 000

STRUCTURAL FORMULA:



FUNCTIONAL CATEGORY:

Tablet disintegrant.

DESCRIPTION:

Crospovidone is a white to creamy white, finely divided, free flowing practically tasteless odorless or nearly odorless, hygroscopic powder.

TYPICAL PROPERTIES:

DENSITY:

1.22g/ cm3.

SOLUBILITY:

Practically insoluble in water and most common organic solvents.

PH (1%SUSPENSION):

5.0-8.0

RESIDUE ON IGNITION:

≤0.4%

MOISTURE CONTENT:

Maximum moisture absorption is approximately 60%.

METHOD OF MANUFACTURE:

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone

is then polymerized in solution, using a catalyst. Crospovidone is prepared by a 'popcorn polymerization' process.

STORAGE CONDITIONS:

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

HANDLING PRECAUTIONS:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves and dust mask are recommended

INCOMPATIBILITIES:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

SAFETY:

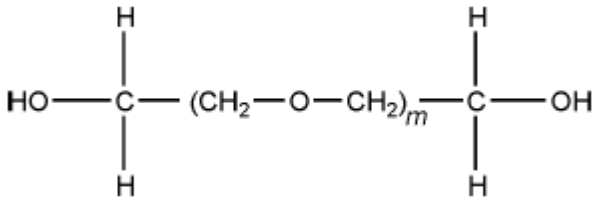
Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO **(Raymond C Rowe et al., 2006).**

PEG-6000

SYNONYM:

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

STRUCTURE:



CHEMICAL NAME:

a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

EMPIRICAL FORMULA:

HOCH2(CH2OCH2)mCH2OH

Where m represents the average number of oxyethylene groups. Alternatively, the general formula H(OCH2CH2)nOH may be used to represent polyethylene glycol, where n is a number m in the previous formula +1.

MOLECULAR WEIGHT:

6000

FUNCTIONAL CATEGORY:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

DESCRIPTION:

The USPNF 23 describes polyethylene glycol as being an addition polymer ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades

1000 and above are solids at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

PROPERTIES:

Physical state	:	white flakes
Solubility in water	:	soluble in water
Solvent solubility:		soluble in methanol, ethanol (95%), dichloromethane and acetone.

HANDLING PRECAUTION:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended**.**

STABILITY AND STORAGE CONDITIONS:

Polyethylene glycols are chemically stable in air and in solution; Polyethylene glycols should be stored in well-closed containers in a cool, dry place.

SAFETY:

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

CROSCARMELLOSE SODIUM

Synonyms:

- Ac-Di-Sol.
- Cross linked carboxymethylcellulose sodium.
- Explocel.
- Modified cellulose gum.
- Primellose.
- Solutab.
- Vivasol.

Chemical Name:

Cross linked carboxy methyl ether Cellulose sodium salt.

Functional Category:

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation:

Disintegrating agent for tablets and capsules.

Description:

-White or grayish white powder.

-Odourless and tasteless.

-Insoluble in water. Practically insoluble in acetone, ethanol and toluene.

Pharmacopoeial Specifications:

pH (1% w/v dispersion) 5.0–7.0

Loss on drying≤10%

Heavy metals≤10 ppm

Sodium chloride and sodium glycolate≤ 0.5%

Sulfated ash 14.0–28.0%

Settling volume 10.0–30.0 ml

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.

Density (bulk): 0.529 g/cm3

Density (tapped): 0.819 g/cm3

Density (true): 1.543 g/cm3

Stability and Storage Conditions:

Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Handling Precautions:

Croscarmellose sodium may be irritant to the eyes; eye protection is recommended (Hand book of Pharmaceutical excipients-5th edition, 211-213).

SODIUM STARCH GLYCOLATE

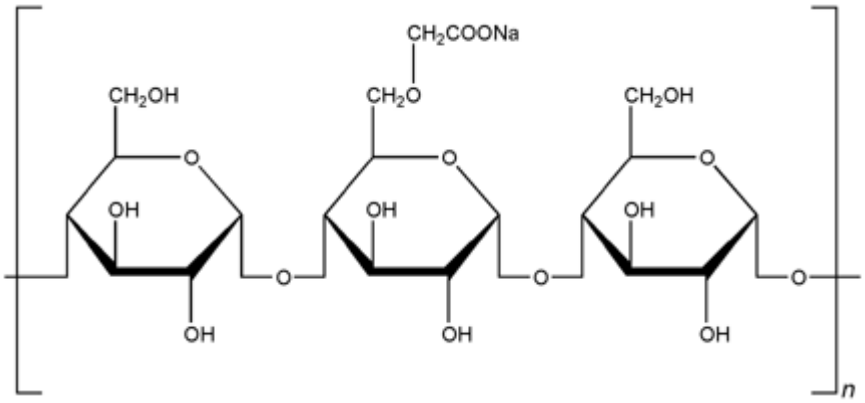
Synonyms:

- Explosol.
- Explotab.
- Primojel.
- Starch carboxymethyl ether, sodium salt.
- Tablo.
- Vivastar P.

Chemical Name:

Sodium carboxymethylstarch.

Chemical structure:



Functional Category:

Tablet and capsule disintegrant.

Application in Pharmaceutical Formulation:

- Sodium starch glycolate is used as a disintegrant in capsule and tablet formulations.
- Sodium starch glycolate is also used as a suspending vehicle.

Description:

- Sodium starch glycolate is a white to off-white, odorless, tasteless, free flowing powder
- It does not melt, but chars at approximately 200^{o}C
- It is sparingly soluble in ethanol (95%) but practically insoluble in water.

Pharmacopoeial Specifications:

- Specific surface area: 0.24m2/g;
- Swelling capacity: In water, sodium starch glycolate swells to up to 300 times its volume.
- Viscosity (dynamic): 4200 mPa s (200 cP) for a 4% w/v aqueous dispersion.
- Viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion.

Stability and Storage Conditions:

Sodium starch glycolate should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Handling Precautions:

Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended (Hand book of Pharmaceutical excipients-5th edition).

MAGNESIUM STEARATE

Synonyms:

- Magnesium octadecanoat.
- Octadecanoic acid, magnesium salt.
- Stearic acid, magnesium salt.

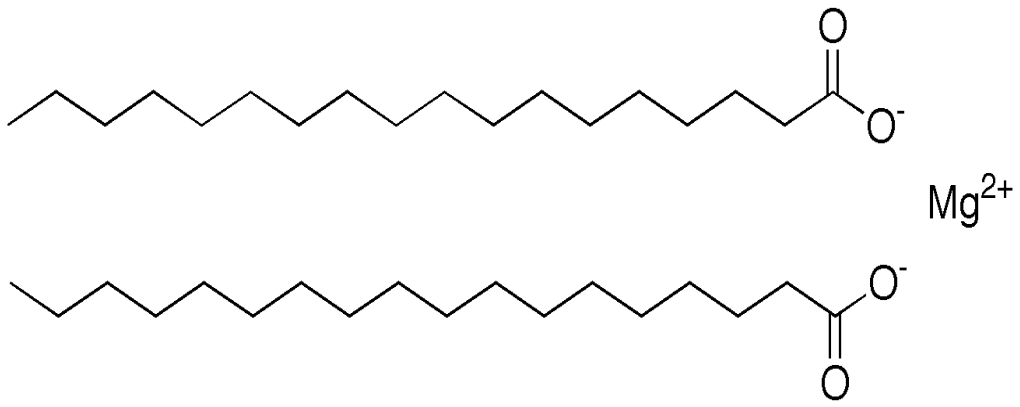
Chemical Name:

Octadecanoic acid magnesium salt.

Structural Formula:

$[CH_3 (CH_2)_{16}COO]_2Mg$

Molecular Structure:



Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$& 591.34

Functional Category:

Tablet and capsule lubricant.

Application in Pharmaceutical Formulation:

- Lubricant in capsule and tablet formulation.(0.25% to 0.25%).

- ❖ Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- ❖ It is also used in barrier creams.

Description:

- ❖ Magnesium stearate is a very fine, light white powder.
- ❖ Faint odour.
- ❖ Characteristic taste.
- ❖ Greasy to the touch and readily adheres to the skin.

Pharmacopoeial Specifications:

Freezing point	5538C
Nickel	45 ppm
Cadmium	43 ppm
Loss on drying	46.0%
Chloride	40.1%
Sulfate	41.0%
Lead	410 ppm

Stability and Storage Conditions:

Magnesium stearate should be stored in a wellclosed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety:

Oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Handling Precautions:

- Eye protection and gloves are recommended.

-Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking (Hand book of Pharmaceutical excipients-5th edition, 430-433).

MANNITOL

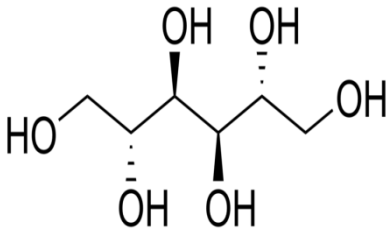
Synonyms:

- Cordycepic acid.
- Manna sugar.
- D-Mannite.
- Pearlitol.

Chemical Name:

D-Mannitol.

Chemical structure:



Empirical Formula and Molecular Weight:

$C_6H_{14}O_6$ & 182.17

Functional Category:

- Diluent.
- Sweetening agent.
- Tonicity agent.

Application in Pharmaceutical Formulation:

- Mannitol is widely used in pharmaceutical formulations and food products.
- It is used asdiluents (10–90% w/w) in tablet formulations.

- ❖ Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations.
- ❖ Plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulation.
- ❖ It is used as a carrier in dry powder inhalers.
- ❖ It is also used asdiluents in rapidly dispersing oral dosage forms.
- ❖ It is used in food applications as a bulking agent.

Description:

- ❖ Mannitol is a white, odorless, crystalline powder, or free-flowing granules.
- ❖ It has a sweet taste.
- ❖ Microscopically, it appears as orthorhombic needles when crystallized from alcohol.
- ❖ Mannitol shows polymorphism.

Pharmacopoeial Specifications:

- ❖ Density (bulk):0.430 g/cm3.
- ❖ Density (tapped):0.734 g/cm3.
- ❖ Density (true): 1.514 g/cm3.
- ❖ Dissociation constant: pKa = 13.5 at 188C.
- ❖ Flowability: powder is cohesive, granules are free flowing.
- ❖ Melting point: 166–168^{o}C
- ❖ Loss on drying: 40.3%

Stability and Storage Conditions:

It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

- Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.
- Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.
- Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Handling Precautions:

Mannitol may be irritant to the eyes; eye protection is recommended..

(Hand book of Pharmaceutical excipients-5th edition,449-453)

MICROCRYSTALLINE CELLULOSE

Synonyms:

- Avicel PH.
- Celex.
- Celphere.
- Ceolus KG.
- Ethispheres.
- Fibrocel.
- Pharmacel.
- Tabulose.
- Vivapur.

Chemical Name:

Cellulose.

Empirical Formula:

$(C_6H_{10}O_5)$ n

Molecular Weight:

36 000

Functional Category:

- Adsorbent.
- Suspendingagent, Tablet and capsule diluents, tablet disintegrant.

Application in Pharmaceutical Formulation:

- Microcrystalline cellulose is used as a binder/diluent in oral tablet and capsule formulations.

- ❖ Microcrystalline cellulose is used as a lubricant and disintegrant agent in tablet formulation.
- ❖ Microcrystalline cellulose is also used in cosmetics and food products.

Description:

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

Use Concentration (%)

- Adsorbent: 20–90
- Antiadherent: 5–20
- Capsule binder/diluent: 20–90
- Tablet disintegrant: 5–15
- Tablet binder/diluents: 20–90

Pharmacopoeial Specifications:

- ❖ pH: 5.0–7.0
- ❖ Loss on drying: 47.0%
- ❖ Residue on ignition: 40.05%
- ❖ Sulfated ash: 40.1%
- ❖ Heavy metals: 410 ppm

Typical Properties:

- Density (tapped):0.478 g/cm3,
- Density (true): 1.512–1.668 g/cm3
- Flowability: 1.41 g/s for Emcocel 90M.
- Melting point: chars at 260–2708C.
- Microcrystalline cellulose is hygroscopic.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Handling Precautions:

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended (Hand book of Pharmaceutical excipients-5th edition, 132-135).

TALC

Synonyms:

Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate, MagsilOsmanthus, Magsil Star, powdered talc, purified French chalk, Purtalc, soapstone, steatite, Superiore.

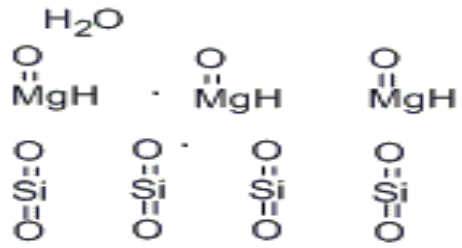
Chemical Name:

Talc

Empirical Formula:

$Mg_6(Si_2O_5)_4(OH)_4$.

Chemical Structure:



Functional Category:

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Applications in Pharmaceutical Formulations:

- Lubricant and diluents.
- Dissolution retardant in the development of controlled-release products.
- An adsorbant.
- Dusting powder.

- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.
- Dusting powder: 90.0–99.0%
- Glidant and tablet lubricant: 1.0–10.0%
- Tablet and capsule diluents: 5.0–30.0%

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Pharmacopoeial Specifications:

- Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.
- Hardness (Mohs): 1.0–1.5
- Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.
- Specific gravity: 2.7–2.8
- Specific surface area: 2.41–2.42m2/g

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Handling Precautions:

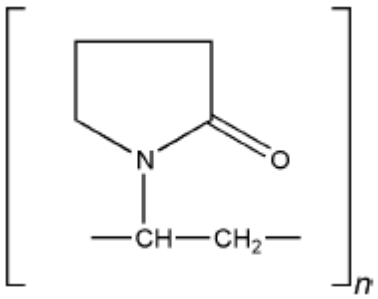
Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. In the UK, the occupational exposure limit for talc is 1 mg/m3 of respirable dust long-term (8-hour TWA).Eye protection, gloves, and a respirator are recommended (Handbook ofPharmaceutical excipients- 5th edition, 641-643).

PVP K 30

SYNONYM

- Kollidon
- Plasdone
- poly[1-(2-oxo-1-pyrrolidinyl)ethylene]
- Polyvidone;Polyvinylpyrrolidone
- PVP; 1-vinyl-2-pyrrolidinone polymer.

STRUCTURE



CHEMICAL NAME

1-Ethenyl-2-pyrrolidinone homopolymer

EMPIRICAL FORMULA

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, in the range 10–120.

The K-value is calculated using Fikentscher's equation:

$$\log z = c \left[\frac{75k2}{1+1.5kc} \right]$$

Where z is the relative viscosity of the solution of concentration c (in % w/v), and k is the K-value $\times 10^{-3}$

MOLECULAR WEIGHT : 50000

FUNCTIONAL CATEGORY:

Disintegrant; dissolution aid; suspending agent; tablet binder

DESCRIPTION:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

PROPERTIES

Physical state	:	white powder
Solubility	:	freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

HANDLING PRECAUTIONS:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended

STABILITY AND STORAGE CONDITIONS:

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

SAFETY:

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.

Additionally it has no irritant effect on the skin and causes no sensitization (Handbook of Pharmaceutical excipients- 5th edition, 641-643).

CHAPTER IX

EXPERIMENTAL PROTOCOL

CHAPTER IX

EXPERIMENT PROTOCOL

I. PREPARATION OF STANDARD CALIBRATION CURVE:

a) Determination of λ max for ormeloxifene in distilled water and phosphate buffer pH (6.8):

Ormeloxifene solution 10 µg/ml in distilled water and phosphate buffer pH 6.8 solution is prepared then scanned by a UV spectrophotometer at wavelengths ranging from 400nm to 200nm, the λmax for solution was determined (Abd Al Hammid., et al, 2013).

b) Calibration of ormeloxifene in distilled water and phosphate buffer pH (6.8):

An accurately weighed quantity (100mg) of pure drug Ormeloxifene.Hcl is dissolved in sufficient amount of methanol and made up to 100ml with Distilled water to produce 1mg/ml solution. From this 10ml of the solution is pipette-out and made up to 100ml with distilled water. From this 5-25ml is pipette-out and diluted to 100ml with distilled water. The solution is scan within the range of 200nm-400nm in UV-Spectrophotometer. The absorbance of the solutions is measured at 278nm by using UV spectrophotometer and distilled water was used as blank solution. The calibration graph is drawn by taking concentration in X-axis and respective absorbance in Y-axis to get a straight line as per Beers law.

c) Calibration of ormeloxifene with phosphate buffer pH 6.8

Preparation of pH 6.8 Phosphate Buffer Solution:

50 ml of monobasic 0.2M Potassium phosphate solution in 200ml volumetric flask and added 22.4ml of 0.2 m sodium hydroxide then added water to make up the volume.

Preparation of 0.2 M Monobasic potassium phosphate solution

Dissolved 27.22g of monobasic potassium phosphate in water and dilute with water to 1000ml. (Indian pharmacopeia 2010).

An accurately weighed quantity (100mg) of pure drug Ormeloxifene.Hcl is dissolved in sufficient amount of methanol and made up to 100ml with pH 6.8 phosphate buffer to produce 1mg/ml solution. From this 10ml of the solution is pipette-out and made up to 100ml with distilled water. From this 5-25ml is pipette-out and diluted to 100ml with distilled water. The solution is scan within the range of 200-400 nm in UV-Spectrophotometer. The absorbance of the solutions is measured at 278nm by using UV spectrophotometer and phosphate buffer pH 6.8 was used as blank solution. The calibration graph is drawn by taking concentration in X-axis and respective absorbance in Y-axis to get a straight line as per Beers law (Abd Al Hammid., et al, 2013).

II. COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS:

Compatibility studies are carried out to confirm there are no interactions existing between the drug and excipients. It gives information needed for selection of excipients with the drug for the formulation of solid dispersion. Infrared

spectrophotometry and Differential scanning calorimetry studies are the two techniques used to check the compatibility studies between drug and polymers.

1) **Differential Scanning Colorimetric(DSC) studies:**

The possibility of drug-polymer interaction was investigated by Differential scanning calorimetry (DSC 200 TA Instruments, USA). The DSC thermograms of pure drug and the polymers were recorded to study the interactions between drug and polymers. The samples were separately sealed in aluminium cells and set in a thermal analyzer. The thermal analysis was performed at a scanning rate of 10 ^{0}C per minute over a temperature range of 50-200 (Abdul Hasan Sathali A, and Selvaraj V, 2012)

2) **Fourier Transform-Infra Red (FT-IR) Studies:**

Ormeloxifene and β-cyclodextrin are subjected to Fourier Transform Infra Red Spectroscopy studies (Shimadzu,Japan).Samples are prepared using KBr disc method and spectra are recorded over the range 600-4500 per cm. Spectra are analyzed for drug-carrier interaction and functional groups involved in the complexation process (Hyma P., et al, 2012).

III. FORMULATION AND EVALUATION OF SOLID DISPERSIONS.

a) Formulation and evaluation of solid dispersion

Solid dispersion of Ormeloxifene hydrochloride is prepared by following methods

i) Kneading method

ii) Melting method

iii) Co precipitation method

iv) Solvent evaporation method

v) Physical mixture

i) Kneading method

Ormeloxifene with β-cyclodextrin in the molar ratio of 1:1, 1:2, 1:3 and 1:4 was taken in a clean glass mortar. First, β-cyclodextrin was placed in a mortar; a small quantity of 50% methanol was added to it while triturating to get slurry like consistency. Then the drug was slowly incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25°C for 24 hours, pulverized, passed through sieve # 100 and stored in desiccators over fused silica gel (Prabhakar Shirse., et al., 2012).

ii) Melting method

Water soluble carriers PEG 6000 are taken in a china dish and heated at 60ºC in a water bath, until the mixture melts completely. The drug (Ormeloxifene) is added to the molten polymer and mixed thoroughly. The dispersion is cooled to ambient condition. Solidified mass is crushed, pulverized and passed through sieve No. 120 and stored in desiccators (Abdul Hasan Sathali.A and Selvaraj.V, 2012).

iii) Co precipitation method

20%w/w solution of ß-cyclodextrin(BCD) was prepared at 75°C.An appropriate amount of the drug Ormeloxifene calculated according to the selected drug:BCD molar ratio (1:1, 1:2, 1:3, and 1:4) was then added to the solution, which was cooled to room temperature while continuously stirring and shaking. During cooling, the solid drug ß-cyclodextrin complex precipitated (Deepthi Mathew et al., 2009).

iv) Solvent evaporation method

Ormeloxifene and the polymer [PEG – 6000] as per the ratio of 1:1, 1:2, 1:3, and 1:4 were dissolved in a minimum amount of methanol. The solvent was removed by evaporation on magnetic stirrer at the temperature 40°C for 1hr. The resulting residue was dried for 2 hour and stored overnight in desicators. After drying, the residue was ground in a mortar and sieved through a mesh # 60. The resultant solid dispersions were stored in desiccators until further investigation (Abhilash M *et al.,* 2013).

v) Physical mixture

Ormeloxifene and ß-cyclodextrin (BCD) in 1:1, 1:2, 1:3 and 1:4 molar ratio were homogeneously blended in glass mortar for 1 hour and passed the blended through sieve no. 60, dried and finally stored in a desiccators (Shukla Vikesh et al., 2009).

b) Estimation of Percentage Yield

Percentage yield is calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions are collected and weighed to determined practical yield from the following formula (Kadam N.R., et al, 2010).

$$\text{Percentage Yield} = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoretical mass (drug +carrier)}} \times 100$$

c) Determination of Drug Content

The physical mixtures and solid dispersions equivalent to 10mg of Ormeloxifene hydrochloride are weighed accurately and dissolved in 10ml of methanol. The solution is filtered, diluted suitably with distilled water and drug content is analyzed at λ_{max} by UV –Spectrophotometer (Abdul Hasan Sathali.A and Selvaraj.V., et al, 2012).

$$\% \text{ Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

d) *In vitro* Dissolution Studies

In vitro dissolution studies of Ormeloxifene hydrochloridel in pure drug form, physical mixtures and solid dispersions (SDs) are performed by using dissolution test apparatus (USP type II) at the paddle rotation speed of 50 rpm in 900ml of distilled water and temperature is maintained at 37°C± 0.5 °C. Samples equivalent to 10mg of Ormeloxifene hydrochloride is filled in hard gelatin capsules used for dissolution studies. Samples are collected at regular interval of time (10, 20, 30, 40, 50, 60 min). The absorbance of the samples is measured at λ_{max} after suitable dilution using appropriate blank**.** The dissolution experiments are conducted in triplicate (Kadam N.R., et al, 2010).

e) Selection of best formulation

The selection of best formulation is done based on rate of ormeloxifene release by *invitro* dissolutio release studies.

IV. EVALUATION OF SELECTED FORMULATION

a) Powder X Ray Diffraction Studies (PXRD)

Powder X-ray diffraction patterns (XRD) of the pure drug, and solid dispersion (K 4) are recorded with an X-Ray Diffractometer (XD, Shimadzu, Japan) using copper as x-ray target, a voltage of 40 KV, a current of 30 mA and withn1.5404 angestron wavelength.. The diffraction patterns run at 2.4 degree / min over the 2θ range of 2-50 degree. (Abdul Hasan Sathali.A and Selvaraj.V., 2012)

b) **Fourier Transform Infrared spectroscopic study**.

The possibility of drug-excipient interactions are further investigated by FT-IR. The FT-IR graph of pure drug and combination of drug with excipient are recorded .The analysis is performed by using Shimadzu FT-IR Spectrometer. The scanning range was 450-4000 cm^{-1} and the resolution was $4cm^{-1}$. Samples were prepared in KBr pellets. (Kothawade.S.N., et al, 2010).

c) Solubility Studies

Solubility study is assessed out according to the method of Higuchi and Cannors. The solubility of racecadotril as pure drug, physical mixture and solid dispersion (K 4) are determined in distilled water and acid buffer PH 6.8. Samples are equivalent to 10mg of drug is taken and to this 10ml of respective medium is being added in 250ml conical flask, and shaken for 24 hours at room temperature on Rotary Flask Shaker. The entire samples are protected from light by wrapping the flask by aluminum foil. After 24 hours samples are filtered through whatman filter paper and aliquots are suitably diluted and assayed by spectrophotometrically at 278nm.(Abdul Hasan Sathali.A and Selvaraj.V.,2012)

V. PREFORMULATION STUDY FOR FAST DISSOLVING TABLETS

1) Angle of Repose:

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder.

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan(\theta) = \tan^{-1}(h / r)$$

Where,

θ is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property (Debjit Bhowmik et al., 2009).

2) Bulk Density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by (Debjit Bhowmik et al ., 2009)

$$Db = M / V_b$$

Where, M is the mass of powder, V_b is the bulk volume of the powder.

3) Tapped Density:

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by (Debjit Bhowmik et al., 2009)

$$\mathbf{Dt = M / Vt}$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

4) Percentage of compressibility (or) Carr's index:

It indicates powder flow properties. It is expressed in percentage and is give

$$\mathbf{I = \frac{D_t - D_b}{D_t} \times 100}$$

Where,

Dt is the tapped density of the powder

D_b is the bulk density of the powder.

Relationship between % compressibility and flowability

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

5) Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the followingformula (Debjit Bhowmik et al., 2009).

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where,

Dt- is the tapped density.

Db-is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

6) Precompression drug Content:

10mg equivalent of Ormeloxefine drug complex was dissolved in sufficient amount of methanol and made upto 100ml of distilled water. From this solution 10ml was pipette out into 100ml volumetric standard flask and volume was made to 100ml with distilled water. The absorbance of the solution is measured at 278nm using

distilled water as blank and the content of ormeloxefine is estimated.(Imran Shekh and et al, 2011)

VI) FORMULATION OF ORMELOXIFENE FAST DISSOLVING TABLETS

Fast dissolving/disintegrating tablets were prepared by using best resultant solid dispersion product K-4 [kneading mixture 1:4 molar ratio of Ormeloxifene HCl and ß- cyclodextrin]. The drug complex equivalent to 30 mg ormeloxifene with variable concentration of superdisintegrants, microcrystalline cellulose, talc,magnesium streate, pvp k-30 and mannitol (for cooling effect and diluents) in Powder blend equivalent to 250 mg of average tablet weight.

An accurately weighed quantity of kneading mixture (drug-carrier complex) is mixed with different ratio of superdisintegrant (Sodium starch glycolate, Crospovidone, CroscarmelloseSodium), microcrystalline cellulose and Mannitol, in geometrical dilution method. Then Magnesium stearate and Talc are added, mixed thoroughly and compressed into tablets by using single punching tablet machine to produce flat faced tablets. The average tablet weight is 250mg, with 8mm diameter. The compositions of the different formulations are given in Table (Sawarikar P.P *et al.*, 2010).

VII) POST COMPRESSION EVALUATION OF FAST DISSOLVING TABLET

1) Thickness and diameter

Tablet thickness and diameter can be measured using a simple procedure. 5 tablets were taken and their thickness and diameter was measured using Varnier calipers (Amit Modi, 2012).

2) Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time (Debjit Bhowmik et al., 2009).

3) Weight variation test

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in the table (Debjit Bhowmik et al., 2009).

Average weight of tablet	% Deviation
80mg or Less	±10
More than 80mg but less than 250mg	±7.5
250mg or more	±5

4) Friability test:

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula. (Debjit Bhowmik et al ., 2009**)**

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

5) Uniformity of Drug Content:

Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 10mg of Ormeloxefine was weighed and dissolved in methanol, the volume was made up to 100ml with pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, The absorbance was measured at wavelength 278nm using UV-Visible spectrophotometer.Content uniformity was calculated using formula (Amit Modi, 2012).

$$\% \text{ Purity} = \frac{\text{Absorbance of unknown (Au)}}{\text{Absorbance of Standard (As)}} \times 10\ C$$

Where,

C – Concentration

6) *Invitro* drug release studies:

Dissolution studies of all tablets were performed using dissolution tester (Paddle type, LABINDIA 2000, India). Tablets were added to the 900 ml of Phosphate buffer pH 6.8 at 37°C ± 0.5°C, which was stirred with a rotating paddle at 50 rpm. 5ml samples were withdrawn from the dissolution apparatus at the time in travel of 5, 10, 15, 20, 25, 30, 40, 50, and 60mins, equal volume of fresh medium was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Assay carried out using UV spectrophotometer (Shimdzu 1700 UV/Visible Spectrophotometer, Japan) at 278nm.(Indian pharmacopeia, 2010)

7) Solubility studies

Solubility study is assessed out according to the method of Higuchi and Connors. The solubility of Ormeloxifene pure drug, kneading mixture and Fast dissolving tablets are determined in distilled water, phosphate buffer pH 6.8 and acid buffer pH 1.2. Samples equivalent to 10 mg of drug is taken and to this 10 mL of respective medium is being added in 250 mL conical flask, and shaken for 24 hours at room temperature on rotary flask shaker (Secor, India). The entire samples are protected from light by wrapping the flask by aluminum foil. After 24 hours samples are filtered through whatmann filter paper No. 42 and aliquots are suitably diluted and assayed by spectrophotometrically at 278 nm (Abdul Hasan Sathali A and Selvaraj V., 2012).

8) Disintegration time

The test was carried out on 6 tablets using the apparatus specified in IP 2010 distilled water at $37^{o}C \pm 2^{o}C$ was used as a disintegration medium and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in second (Shallesh Sharma et al., 2008)

9) Water Absorption Ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation (Debjit Bhowmik et al., 2009).

$$R=10 (wa/wb)$$

where,

Wb is weight of tablet before water absorption

Wa is weight of tablet after water absorption.

10) Wetting Time:

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. (Debjit Bhowmik et al., 2009).

VIII. BEST FORMULATION SELECTION

Among twenty formulations, formulation the best was selected on the basis of lowest disintegration time and highest drug release profile, high water absorption ratio, low wetting time and minimum chemicals composition (Mangesh M.Kumare., et al, 2013).

IX) STABILITY STUDY (Temperature Dependent)

The fast dissolving tablet stored under following conditions for a period prescribed by ICH guidelines for accelerated studies. 40 ± 1^0 C, 50 ± 1^0C and 37 ± 1^0 C &RH 75 %± 5 %. The tablets were withdrawn a period of 15 days and analyzed for physical characterization such as visual defects, hardness, Friability, disintegration and Dissolution etc. the data plotted into first order equations to determine the kinetics of degradation (Shallesh Sharma et al., 2008).

CHAPTER X

RESULTS AND DISCUSSION

TABLES & FIGURES

CHAPTER X

RESULTS AND DISCUSSION

1. PREPARATION OF STANDARD CALIBRATION CURVE

a) Determination of λ-max for Ormeloxifene in Distilled water and phosphate buffer pH (6.8):

The absorption maximum ($\lambda_{max)}$ of the ormeloxifene was estimated by scanning the drug solution (10µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λ_{max}) was 278nm in distilled water and phosphate buffer pH 6.8, which was shown **in Figure 1** (Anilkumar Shinde J *et.al.*, 2010).

b) Calibration of ormeloxifene hydrochloride in distilled water:

The Standard Calibration curves of ormeloxifene hydrochloride were prepared using distilled water. The absorbances were measured at λ_{max} of 278nm. The correlation coefficient was found to be 0.9997. Ormeloxifene hydrochloride obeys the beer's law within the concentration range of (5-25µg/ml). Calibration plot of ormeloxifene in distilled water was shown in **Table 1(a)** and **Figure 2 (a).**

c) Calibration of ormeloxifene in phosphate buffer pH (6.8):

The Standard Calibration curves of ormeloxifene hydrochloride were prepared using pH.6.8 phosphate buffer. The absorbances were measured at λ_{max} of 278nm. The correlation coefficient was found to be 0.9996. Ormeloxifene hydrochloride

obeys the beer's law within the concentration range of (5-25µg/ml). Calibration plot of ormeloxifene in ph 6.8 buffer was shown in **Table 1 (b)** and **Figure 2(b).**

II. COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS:

1) Fourier Transform Infrared Spectroscopic studies:

FT-IR spectrum of the pure drug, PEG 6000, Betacyclodextrin and physical mixtures was recorded. Pure Ormeloxifene hydrochloride spectra showed sharp characteristic peaks at 2929.97, 1619.29, 1507.42, 1157.33, and 608.55 cm^{-1}**[Figure 27 (a), 27 (e), 27 (h), 27 (n), 27 (q)].** All the above characteristic peaks appear in the IR spectrum of physical mixtures indicates that there is no modification or interaction between drug and carriers (Deshmukh D.B. *et al*., 2010).

III. FORMULATION AND EVALUATION OF SOLID DISPERSIONS

a) Formulation of solid dispersions:

In the present study, 16 formulations of ormeloxifene hydrochloride solid dispersions were prepared by using carriers like betacyclodextrin and PEG6000 in the ratio of 1:1, 1:2, 1:3 and 1:4 in four methods (Kneading method, Melting method, Co precipitation method and Solvent evaporation method) **(Table 2)** .The prepared solid dispersions were found to be uniform and homogeneous in appearance.

Betacyclodextrin carrier was used for kneading and co precipitation method of formulation, PEG6000 used in melting and solvent evaporation method formulations.

b) Estimation of Percentage Yield:

The percentage yield of all the formulations was determined by weighing the practical yield. Percentage yield is calculated for all the formulations including physical mixture **(Table 3)**. The percentage yield of solid dispersions ranged from 83.6% - 96.88%. The percentage yield of the solid dispersion M3 was found to be

high (96.88%) as compared to the other formulations. Similarly the percentage yield of physical mixture ranged from 97.66 % - 98.39% which indicates that there is no considerable loss in the yield during the physical mixing process (Abhilash. M., *et al.* 2013).

c) Determination of Drug Content:

The drug content in all the formulations was estimated spectrophotometrically at 278 nm (Shimadzu UV1700, Japan). The drug content of the prepared solid dispersions was found to be in the range of 84.39 % to 95.40% indicating the uniform distribution of drug in the formulation**. (Table 4)** (Abhilash. M., *et al.* 2013).

d) *In vitro* Dissolution Studies:

The cumulative percentage drug release profile data obtained for all solid dispersion formulations and physical mixture are tabulated in **Table no 5, 6, 7, 8 and 9.** The cumulative percentage of drug release of pure drug (Ormeloxifene hydrochloride) at the end of one hour was found to be 40.90% **(Figure 3).**

In kneading method, betacyclodextrin was used as a carrier. The release profiles of formulation in the ratios of 1:1, 1:2, 1:3, and 1:4 were found to be 55.09% (K1), 68.59%(K2), 75.97%(K3), and 91.77 % (K4) after 1 hour **(Figure 4)**. From the results, it was observed that K4 (1:4 ratio) exhibits maximum drug release of 91.77% and it was rated as the best formulation in kneading method using betacyclodextrin.

In Melting method, PEG- 6000 was used as a carrier. The release profile of PEG 6000 in the ratios of 1:1 ,1:2, 1:3,and 1:4 were found to be 42.18 % (M1), 44.32 % (M2), 56.90 % (M3), and 63.45 % (M4) after 1 hour **(Figure 5).** From the results, it was observed that M4 (1:4 ratio) exhibits maximum release of 63.45 % and it was rated as the best formulation in melting method using PEG 6000. In

Coprecipitation method, betacyclodextrin was used as a carrier. The release profile of BCD in the ratios of 1:1 ,1:2, 1:3,and 1:4 were found to be 46.09 %(C1), 55.56 %(C2), 66.66 %(C3),and 81.75 %(C4) after 1 hour**(Figure 6).** From the results, it was observed that C4 (1:4 ratio) exhibits maximum release of 81.75 % and it was rated as the best formulation in Co precipitation method using BCD.

In Solvent evaporation method, PEG- 6000 was used as carrier. The release profiles of PEG - 6000 ,in the ratios of 1:1, 1:2, 1:3,and 1:4 was found to be 46.10%(S1), 49.67 %(S2),54.20%(S3),and 70.57 %(S4) after 1 hour **(Figure 7).**

From the results it was observed that the release profile of K-4 (1:4 ratio) is higher than the release profiles of other formulations in this method.

Comparision of methods

The invitro results indicated that the method of formulation influences the drug releases. Solid dispersion prepared with betacyclodextrin by kneading and co precipitation method. Kneading method, was found to be the best release rate of 91.77 % (K-4) **(Figure 8)** at 1 hour**,** compared with the release profile of copercipitation method 81.75 %(C-4). The solid dispersion prepared by using PEG-6000 by melting and solvent evaporation method, the solvent evaporation method was found to be the best with the release rate of 70.57 % (S-4) **(Figure 9)** at 1 hour**,** compared with the release profile of melting method 63.45 % (M-4).

The physical mixture of drug with different carriers like betacylodextrin and PEG–6000 were prepared in 1:4 ratio was found to be the best release rate of 77 % by using betacyclodextrin (PB-4) **(Figure 10)** at 1 hour**,** compared with the release profile of PEG 6000 was 63.89 % (PP-4).

The comparison of *In-vitro* drug release profile was shown in **Figure 11**. From the results it was observed that the release profile of K-4 prepared by kneading method was higher release profile than other formulations. So this was considered to be one of the best method for preparing ormeloxifene solid dispersion formulation.

e) Selection of Best Formulation:

The best formulation is selected based on the results obtained from the drug *invitro* release studies.

Invitro dissolution studies revealed that there is marked increase in the dissolution rate of Ormeloxifene hydrochloride from all the solid dispersions when compared to physical mixture and pure drug.

From the result it was observed that, between the two carriers, betacyclodextrin ratio was found to have greater release rate than other carrier used **(Figure 12).** The K-4 formulation (kneading method) containing drug and betacyclodextrin (1:4 ratio of drug: carrier) showed higher dissolution rate of 91.77% after 1hour, so it was considered as the overall best formulation **(Figure 13).**

The order of drug release profile is

Pure drug < Physical mixture < Solid dispersion

The drug dissolution was increase in both, physical mixtures and solid dispersion product. It happens because of the enhanced wettability, hydrophilic nature of the carriers and possibility of reduced crystallinity of the drug and conversion of amorphous form of the drug. Solid dispersion product was homogeneously distributed within the carrier in an amorphous state and no drug crystallizes out of the dispersion,

suggesting that drug and polymer exist in the form of a mixture rather than the reaction product (Imran Shekh., etal, 2011).

This study was planned to continue with best resultant product, various superdisintegrants and other excipients to formulate as fast dissolving tablets. The formula as on **Table No 11(a) and 11(b).**

IV.EVALUATION OF SELECTED FORMULATION:

a) Powder X Ray Diffraction Studies (PXRD):

The XRPD patterns of pure drug (Ormeloxifene), excipients (BCD, Mannitol, MCC, PVP K30, CCS, CP and SSG), Kneading Mixture, and selected formulations (F8) were presented in **(Figure 29a, 29b, 29c, 29d, 29e, 29f, 29g, 29h, 29i and 29j)**.

This result confirmed that the characteristic peaks were still preserved indicating the crystalline state was not changed.

b) Fourier Transform Infrared spectroscopic study:

IR Spectrum of the best formulation (K4- drug and betacyclodextrin 1:4 ratio of drug: carrier) was recorded. The pure Ormeloxifene spectra showed sharp characteristic peaks at 1613.29, 1455.34, 1368.54, 1157.33, 1029.06 and 480.29 cm^{-1}**(Figure 27(u).** All the above characteristic peaks appear in the IR spectrum of the best formulation which indicates that there was no interaction between drug and carriers.

c) Solubility Studies of Solid Dispersions:

The solubility study was conducted with pure drug and selected best solid dispersion (K-4) product by distilled water and phosphate buffer pH 6.8 as shown in **Table 10 and Figure 14.** It was observed that the solid dispersion product (K-4) showed high solubility in water (0.556mg/ml) and phosphate buffer pH 6.8 (0.603mg/ml) as compared to pure drug solubility in water (0.266 mg/ml) and phosphate buffer pH 6.8 (0.3 mg/ml) (Nagesh C. *et al.*, 2010).

d) Differential Scanning Calorimetric (DSC) Studies:

DSC thermogram of the best formulation was recorded. Pure Ormeloxifene exhibits a sharp endothermic peak at 144.95^0C **[Figure 28(a)].** An endothermic peak corresponding to the melting point of pure drug was prominent in best formulation (Kneading Mixture) **[Figure 28(i)]**, which suggested clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form.

V) PREFORMULATION STUDY FOR FAST DISSOLVING TABLETS:

1) Angle of Repose:

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of all the formulations ranged from 20˚.88' to 29˚.16'.The results indicated that all the formulations exhibited good flow properties. The results of angle of repose for all the formulations were shown in **Table12** and **Figure 15.**

2) Bulk density:

The bulk density was used to determine the free flowing properties of powder blend. The bulk density of all the formulations was in the range of 1.16 - 1.25g/$cm^{3.}$ The values of bulk density showed that the blend was not tightly packed and indicated

good flow properties. The results of bulk density for all the formulations were shown in **Table 12** and **Figure 16**.

3) Tapped Density:

The tapped density was used to access the free flowing properties of powder blend. The tapped density of all the formulations were in the range of 1.34-1.48 g/cm^3.The results indicated that the blends of all the formulation had good flow properties. The results of tapped density for all the formulations were shown in **Table 12** and **Figure17**.

4) Carr's Compressibility Index:

The carr's compressibility index was used to access the free flowing properties of powder blend. The compressibility index of all the formulations ranged from 11.34 -15.8 %.This value below 16% indicates a powder having good flow property and good propensity of compression. The results of compressibility for all formulations were shown in **Table 12**and **Figure18**.

5) Hausner's Ratio:

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from 1.15-1.19. It was less than 1.25 indicated better flow property of blend. The results of Hausner's ratio for all the formulations were shown in **Table 12**and **Figure19**.

6) Pre compression drug Content:

The drug content of the tablets was used to ensure the therapeutic dosage of the active ingredient in the formulation. The drug content of all the formulation was in the range of 97.03 – 99.6 %.The results indicated all the formulations were within the acceptable limits as per USP. The results were shown in **Table13**.

7) Compatibility studies for drug and tablet excipients:

i) Fourier Transform Infrared Spectroscopic studies:

IR Spectrum of the best formulation (K4- drug and betacyclodextrin 1:4 ratio of drug: carrier), SSG, CCS, CP, PVP K30, MCC and physical mixtures was recorded. The pure Ormeloxifene spectra showed sharp characteristic peaks at 2929.97, 1619.29, 1507.42, 1157.33, and 608.55 cm^{-1} **[Figures 27(b), 27(c), 27(d), 27(f), 27(g), 27(i), 27(j), 27(k), 27(l), 27(m), 27(o), 27(p), 27(r), 27(s), 27(t) and 27(v)].** All the above characteristic peaks appear in the IR spectrum of the best formulation (K4) which indicates that there was no interaction between drug and carriers.

VI) FORMULATION OF ORMELOXIFENE FAST DISSOLVING TABLETS:

The fast dissolving tablet of ormeloxifene was prepared by direct compression method using resultant product of solid dispersion and different ratio (5%, 10%, and 15%) of superdisintegrants (Sodium starch glycolate, Crospovidone and Croscarmellose sodium). The compositions of the different formulation were given in **Table 11 (a) & 11(b)**. Twenty formulations (F1 to F20) were prepared as per formula designed. All the tablets were light white colour and round in shape having 8 mm diameter.

VII) POST COMPRESSION EVALUATION:

The prepared tablets were evaluated on various parameters such as thickness and diameter, hardness, weight variation, friability, uniformity content, wetting time, water absorption ratio, *In-vitro* disintegration time and *In-vitro* dissolution test. The results were summarized in **Table 13 & 14**.

1) Thickness and Diameter:

The thickness and diameter of all the formulations were used to determine the uniformity of size and shape of the tablets. From the results it was found that the thickness of the tablet in all formulation was 3.5- 3.7 mm and the diameter of the tablet in all formulation was 8mm.The results indicating all the formulations had uniform size and shape. The results were shown in **Table 13**.

2) Hardness:

The hardness of the tablets was used to determine the resistance capacity of the tablets to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the tablets of all the formulations was found to be 4kg/cm^2.The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in **Table 13**.

3) Weight Variation Test:

The weight variation test was used to ensure the uniformity of the tablet in all formulations. The weight of all the tablets from each formulation was in the range from 245.7 mg to 248.76 mg. It was found all the tablets passed weight variation test, as the percentage weight variation was within the acceptable limits of 7.5%.The results were shown in **Table 13**.

4) Friability test:

Friability test was measured to ensure the mechanical strength of tablet. The results showed that the friability of all the formulation was ranged from 0.56 % to 0.72%.Friability of all the formulation was lesser than 1 % which indicated the tablets had a good mechanical resistance. The results were shown in **Table13**.

5) Uniformity of drug Content:

The uniformity content test was used to determine the uniform amount of active ingredient present in all formulations. The drug content in the content uniformity of all the formulations was found to be in the range of 97.06 % - 99.66 %. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in **Table 13**.

6) In-vitro drug release Studies:

The formulation dissolution profile range at 15minutes from 33.17 % to 80.49 % (table 14). The dissolution drug release rate was found to be comparatively less in formulation containing sodium starch glycolate. The maximum increased in the dissolution drug release rate was observed with the combination of crospovidone, croscarmellose sodium and sodium starch glycolate containing formulation **(figure 20 to 26)**. The order of the dissolution rate with various superdisintegrants was found to be

Combination of disintegrants > crospovidone > croscarmellose sodium > SSG

This study indicated that combination of superdisintegrants was produce better drug release rate than using alone. The formulation containing crospovidone, croscarmellose sodium and sodium starch glycolate was found to be showed dissolution after 15 minutes of dissolution study produce 80.49% which complies with WHO guild line (WHO Uganda., 2009). Many factors contributed for faster drug release rate such as rapid disintegration, smaller particle size, decrease in agglomeration of particles, increased wettability and decreased crystallinity of drug. Among the twenty formulations the formulation code (F-8) was selected, as a best formulation because of its desirable character of low disintegration time and highest

drug release, high water absorption rate, short wetting time and minimum chemicals composition.(Mangesh M.Kumare.,etal, 2013).

7) Solubility studies:

The solubility study was conducted with pure drug, solid dispersion product and best fast dissolving tablet (F-8) using distilled water and phosphate buffer pH 6.8 as shown in **Table 15 & Figure 14.** It was observed that the fast dissolving tablet F-8 (0.79mg/ml) has highest solubility in water and phosphate buffer pH 6.8 (0.81 mg/ml) compared to pure drug in distilled water (0.26mg/ml) and phosphate buffer pH 6.8 (0.3 mg/ ml).

8) Disintegration Time:

The *in-vitro* disintegration time was determined by disintegration test apparatus. The results were shown in **Table 14**.

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19 and F20 showed the disintegration time 166, 145, 88, 129, 86, 72, 155, 58, 70, 137, 148, 127, 123, 87, 86, 143, 126, 146, 129 and 87 seconds respectively. It was observed that Formulation F8 containing Crospovidone (5%), Croscarmellose sodium (5%) and Sodium starch glycolate (5%) containing tablet disintegrate rapidly in a short time (58 seconds).The results of disintegration of all the tablets were found to be lesser than 180 seconds. So all the formulation satisfied the criteria of fast dissolving tablets.

In vitro disintegration study explained that there was decrease in disintegration time with successive addition of superdisintegrant concentration in formulation but comparatively co-processed formulations (combination of superdisintegrants) take least time for disintegration. Such a difference in disintegration time between all these formulations indicates that in co-processed formulation there might be increase in

capillary action of Superdisintegrants which might have led to improved water uptake. (Mangesh M.Kumare.,etal, 2013)

9) Water Absorption Ratio:

The water absorption ratio test was used to ensure the capacity of the superdisintegrant to absorb the water. The results of water absorption ratio of all the formulation were shown in **Table 14**.

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, and F20 showed the water absorption ratio 9.87%, 18.2%, 45.25%, 21.08%, 40.37%, 57.61%, 13.34%, 73.75%, 71.59%, 12.57%, 20.80%, 19.28%, 27.82%, 49.27%, 72.94%, 26.36%, 26.93, 22.68%, 32.09%, and 52% The results showed that as concentration of superdisintegrant increased water absorption ratio was also increased. Formulation F8 containing combined superdisintegrants showed highest water absorption ratio (73.75%) than other formulation.

The reason for high water absorption ratio for F-8 formulation, the combined superdisintegrant action of water wicking mechanism and capillary action into porous network of tablet, resulting rapidly absorbs water into its network than formulation prepared with other combination of superdisintegrants.(Mangesh M.Kumare.,etal, 2013).

10) Wetting Time*:*

Wetting time of the tablet was used to assess the capacity of the tablets to disintegrate by swelling of water. All the formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. The results of wetting time of all the formulations were shown in **Table 14**.

The formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15.F16, F17, F18, F19,and F20showed the wetting time 228, 178, 116, 153, 126, 62,

181, 53, 59, 159, 162, 147, 141, 134, 120, 152, 131, 155, 126, and 99 seconds respectively. The results indicated that as the concentration of superdisintegrant and type of superdisintegrant influences wetting time. Formulation F8 containing crospovidone (5%), sodium starch glycolate (5%), and cross carmellose sodium (5%) shows lesser wetting time than other formulation.

This may be due to fact that superdisintegrant perform their action of Crospovidone capillary action, Croscarmellose sodium wicking and swelling action and Sodium starch glycolate disintegrate the tablet by swelling mechanism, on combine effect of these three leading to shorter wetting time. (Mangesh M.Kumare.,et al, 2013).

VIII. BEST FORMULATION SELECTION:

Among twenty formulations, the best was selected on the basis of lowest disintegration time, rapid drug release profile, higher water absorption ratio, short wetting time. Formulation F-8 showed lowest disintegration tine of 58 seconds, faster drug release rate of 80.49 in 15 minutes, 95.63% in 30 minutes, comparatively high water absorption ratio of 73.75%, short wetting time of 53 seconds and minimum chemicals composition. In those parameter would drive the F-8 formulation as a best comparatively.

IX) STABILITY STUDY (Temperature Dependent):

The stability studies of best formulation is carried out at an ambient temperature and relative humidity(40^{o}C±2^{o}C, RH75%±5%) for a period of 60 days to find out any physicochemical changes in the dispersions as per modified International Conference On Harmonization (ICH) guidelines. Periodically samples are withdrawn

to estimate the drug content. The results are tabulated **(Table-16)** which indicates that there is no significant change in the drug content (Kavitha. R. *et al.,* 2012).

Table 1 (a): Calibration of Ormeloxifene.HCl with Distilled water

S. No	Concentration [µg/ml]	Absorbance
1	5	0.0426 ± 0.002
2	10	0.0860 ± 0.001
3	15	0.1276 ± 0.003
4	20	0.1720 ± 0.002
5	25	0.2180 ± 0.003

γ = 0.9997

Table 1(b): Calibration of Ormeloxifene.HCl with Phosphate buffer pH (6.8)

S. No	Concentration [µg/ml]	Absorbance
1	5	0.0446 ± 0.001
2	10	0.0853 ± 0.003
3	15	0.1353 ± 0.006
4	20	0.1803 ± 0.002
5	25	0.2260 ± 0.005

γ = 0.9996

Table 2: COMPOSITION OF SOLID DISPERSION

S. No	F. Code	Method	Ratio	Composition
1	K1	Kneading	1:1	Drug : BCD
2	K2	Kneading	1:2	Drug : BCD
3	K3	Kneading	1:3	Drug : BCD
4	K4	Kneading	1:4	Drug : BCD
5	M1	Melting	1:1	Drug : PEG 6000
6	M2	Melting	1:2	Drug : PEG 6000
7	M3	Melting	1:3	Drug : PEG 6000
8	M4	Melting.	1:4	Drug : PEG 6000
9	C1	Co precipitation	1:1	Drug : BCD
10	C2	Co precipitation	1:2	Drug : BCD
11	C3	Co precipitation	1:3	Drug : BCD
12	C4	Co precipitation	1:4	Drug : BCD
13	S1	Solvent evaporation	1:1	Drug : PEG 6000
14	S2	Solvent evaporation	1:2	Drug : PEG 6000
15	S3	Solvent evaporation	1:3	Drug : PEG 6000
16	S4	Solvent evaporation	1:4	Drug : PEG 6000
17	PB 3	Physical mixture	1:3	Drug : BCD
18	PB 4	Physical mixture	1:4	Drug : BCD
19	PP 3	Physical mixture	1:3	Drug : PEG 6000
20	PP4	Physical mixture	1:4	Drug : PEG 6000

Table 3: PERCENTAGE OF YIELD

Sl.No	F. Code	Method	Ratio	% of yield
1	K1	Kneading	1:1	83.60 ± 1.07
2	K2	Kneading	1:2	88.33 ± 2.02
3	K3	Kneading	1:3	85.19 ± 1.750
4	K4	Kneading	1:4	96.60 ± 0.77
5	M1	Melting	1:1	91.72 ± 1.79
6	M2	Melting	1:2	95.35 ± 1.60
7	M3	Melting	1:3	96.88 ± 0.31
8	M4	Melting.	1:4	91.44 ± 1.81
9	C1	Co precipitation	1:1	87.45 ± 2.09
10	C2	Co precipitation	1:2	90.08 ± 0.61
11	C3	Co precipitation	1:3	92.72 ± 1.93
12	C4	Co precipitation	1:4	94.82 ± 1.02
13	S1	Solvent evaporation	1:1	90.05± 1.58
14	S2	Solvent evaporation	1:2	93.97± 1.68
15	S3	Solvent evaporation	1:3	94.93 ± 1.40
16	S4	Solvent evaporation	1:4	88.90 ± 0.56
17	PB 3	Physical mixture	1:3	98.36 ± 0.35
18	PB 4	Physical mixture	1:4	98.10 ± 0.44
19	PP 3	Physical mixture	1:3	98.39 ± 0.31
20	PP4	Physical mixture	1:4	97.66 ± 1.15

Table 4: DRUG CONTENT OF SOLID DISPERSION PRODUCT

Sl.No	F. Code	Method	Ratio	Drug content
1	K1	Kneading	1:1	85.01 ± 2.94
2	K2	Kneading	1:2	84.67 ± 1.89
3	K3	Kneading	1:3	84.70 ± 1.39
4	K4	Kneading	1:4	86.54 ± 4.61
5	M1	Melting	1:1	93.26 ± 1.39
6	M2	Melting	1:2	94.17 ± 0.52
7	M3	Melting	1:3	95.40 ± 1.58
8	M4	Melting.	1:4	86.04 ± 2.02
9	C1	Co precipitation	1:1	86.3± 0.81
10	C2	Co precipitation	1:2	84.39 ± 1.83
11	C3	Co precipitation	1:3	88.37 ± 1.39
12	C4	Co precipitation	1:4	88.75 ± 2.929
13	S1	Solvent evaporation	1:1	85.08± 0.59
14	S2	Solvent evaporation	1:2	86.30 ± 1.53
15	S3	Solvent evaporation	1:3	91.74± 0.92
16	S4	Solvent evaporation	1:4	85.65 ± 1.77
17	PB 3	Physical mixture	1:3	93.02± 1.16
18	PB 4	Physical mixture	1:4	94.95 ± 1.77
19	PP 3	Physical mixture	1:3	92.02± 0.93
20	PP4	Physical mixture	1:4	96.27 ± 0.40

Table 5: CUMULATIVE % DRUG RELEASE OF ORMELOXIFENE.HCl USING BETACYCLODEXTRIN CARRIER BY KNEADING METHOD

Time (min)	Percentage of Drug release				
	K1 (1:1 ratio)	K2 (1:2 ratio)	K3 (1:3 ratio)	K4 (1:4 ratio)	Pure Drug
10	12.44 ± 2.59	19.67 ± 2.59	19.99 ± 2.07	18.29 ± 2.14	7.28 ± 1.18
20	16.98 ± 3.10	25.28 ± 3.74	32.74 ± 2.04	40.73 ± 2.09	13.17 ± 1.57
30	26.74 ± 3.60	33.33 ± 3.65	50.56 ± 4.66	62.64 ± 3.08	21.49 ± 0.61
40	40.62 ± 1.59	57.95 ± 1.63	62.87 ± 4.55	79.49 ± 3.73	29.87 ± 1.18
50	51.16 ± 3.95	64.45 ± 4.23	71.54 ± 2.83	87.17 ± 2.08	35.54 ± 1.59
60	55.09 ± 4.91	68.59 ± 5.24	75.97 ± 3.77	91.77 ± 2.09	40.9 ± 1.60

Table 6: CUMULATIVE % DRUG RELEASE OF ORMELOXIFENE.HCl USING BETACYCLODEXTRINCARRIER BY COPRECIPITATION METHOD

Time (min)	Percentage of Drug release				
	C1 (1:1 ratio)	C2 (1:2 ratio)	C3 (1:3 ratio)	C4 (1:4 ratio)	Pure Drug
10	9.00 ± 1.57	14.16 ± 1.19	11.76 ± 2.06	30.33 ± 4.14	7.28 ± 1.18
20	14.22 ± 1.58	21.45 ± 1.59	36.25 ± 4.87	46.99 ± 4.73	13.17 ± 1.57
30	21.18 ± 1.80	29.84 ± 1.59	52.48 ± 8.09	57.57±5.418	21.49 ± 0.611
40	28.52 ± 2.09	38.26 ± 3.17	59.79 ± 4.19	72.32±1.030	29.87 ± 1.18
50	38.65 ± 1.59	47.41 ± 2.77	63.9 ± 3.70	77.21±3.596	35.54 ± 1.59
60	46.09 ± 1.22	55.56 ± 2.69	66.66 ± 3.20	81.75 ± 2.64	40.9 ± 1.60

TABLE 7: CUMULATIVE % DRUG RELEASE OF ORMELOXIFENE.HCl

Time (min)	Percentage of Drug release				
	M1 (1:1 ratio)	M2 (1:2 ratio)	M3 (1:3 ratio)	M4 (1:4 ratio)	Pure Drug
10	7.78 ± 2.86	10.71 ± 3.07	28.60 ± 2.15	23.84 ± 3.23	7.28 ± 1.18
20	11.45 ± 3.63	15.24 ± 2.58	34.59 ± 2.03	34.44 ± 4.73	13.17 ± 1.57
30	15.97 ± 4.79	22.55 ± 1.58	41.17 ± 2.04	41.96 ± 3.11	21.49 ± 0.61
40	25.00 ± 3.24	29.57 ± 1.06	48.43 ± 1.04	48.73 ± 4.15	29.87 ± 1.18
50	35.11 ± 1.62	33.5 ± 2.16	53.13 ± 1.54	56.91 ± 4.81	35.54 ± 1.59
60	42.18 ± 3.63	44.32 ± 3.75	56.90 ± 1.57	63.45 ± 3.80	40.9 ± 1.60

USING PEG 6000 CARRIER BY MELTING METHOD

TABLE 8: CUMULATIVE % DRUG RELEASE OF ORMELOXIFENE.HCl USING PEG 6000 CARRIER BY SOLVENT EVAPORATION METHOD

Time (min)	Percentage of Drug release				
	PB 3 (1:3 ratio)	PB 4 (1:4 ratio)	PP 3 (1:3 ratio)	PP 4 (1:4 ratio)	Pure Drug
10	15.15 ± 3.16	20.31 ± 2.58	11.37 ± 1.60	13.78 ± 2.04	7.28 ± 1.18
20	30.04 ± 3.33	32.14 ± 2.17	17.28 ± 1.20	21.76 ± 3.13	13.17 ± 1.57
30	45.33 ± 1.58	50.20 ± 1.78	28.74 ± 1.60	32.23 ± 2.18	21.49 ± 0.61
40	59.02 ± 1.23	62.18 ± 2.17	42.31 ± 2.59	42.00 ± 2.79	29.87 ± 1.18
50	65.89 ± 2.67	69.41 ± 2.76	54.60 ± 4.75	53.61 ± 3.63	35.54 ± 1.59
60	73.78 ± 1.02	77.00 ± 2.77	62.79 ± 3.71	63.89 ± 4.25	40.9 ± 1.60

TABLE 9: CUMULATIVE % DRUG RELEASE OF ORMELOXIFENE.HCL USING CARRIER BCD AND PEG 6000 BY PHYSICAL MIXTURE

Time (min)	Percentage of Drug release				
	S1 (1:1 ratio)	S2 (1:2 ratio)	S3 (1:3 ratio)	S4 (1:4 ratio)	Pure Drug
10	8.33 ± 1.57	12.1 ± 1.57	14.13 ± 1.56	17.58 ± 2.58	7.28 ± 1.18
20	14.52 ± 1.18	23.61 ± 7.46	22.46 ± 0.56	28.85 ± 0.68	13.17 ± 1.57
30	22.87 ± 3.17	27.09 ± 1.17	32.56 ± 1.81	37.77 ± 2.09	21.49 ± 0.61
40	31.61 ± 2.74	35.49 ± 3.11	40.28 ± 1.18	48.30 ± 2.73	29.87 ± 1.18
50	42.06 ± 3.76	44.61 ± 1.18	48.09 ± 2.39	62.01 ± 2.08	35.54 ± 1.59
60	46.10 ± 2.16	49.67 ± 2.07	54.20 ± 1.61	70.57 ± 2.02	40.9 ± 1.60

TABLE 10: COMPARISION OF SOLUBILITY STUDY OF ORMELOXIFENE.HCl USING DISTILLED WATER AND BUFFER pH6.8

S.NO	Formulation	Distilled water (mg/ml)	BufferPh 6.8 (mg/ml)
1	PURE DRUG	0.266 ± 0.01	0.30 ± 0.01
2	SOLID DISPERSION (K-4) (DRUG:BCD 1:4)	0.556 ± 0.01	0.603 ± 0.01

TABLE 11(a): ORMELOXIFENE FAST DISSOLVING TABLET FORMULA [F1 – F10]

Ingredients	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**	**F 10**
Ormeloxifene Drug complex Equivalent to 30mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg
Microcrystalline cellulose	-	-	-	25mg	25mg	25mg	-	-	25mg	-
Sodium starch glycolate	12.5 mg	25mg	37.5mg	12.5mg	25mg	37.5mg	12.5mg	12.5mg	12.5mg	-
Croscarmellose sodium	-	-	-	-	-	-	12.5mg	12.5mg	12.5mg	12.5mg
Crospovidone	-	-	-	-	-	-	-	12.5mg	12.5mg	-
Polyvinyl Pyrolidone K-30	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg
Magnesium stearate	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg
Talc	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg
Mannitol (Q S up to 250mg)	75mg	62.5mg	50mg	50mg	37.5mg	25mg	62.5mg	50mg	25mg	75mg

TABLE 11(b): ORMELOXIFENE FAST DISSOLVING TABLET FORMULA [F11 – F20]

Ingredients	F 11	F 12	F 13	F 14	F 15	F 16	F 17	F 18	F 19	F 20
Ormeloxifene Drug complex Equivalent to 30 mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg
Microcrystalline cellulose	-	-	25mg	25mg	25mg	25mg	25mg	-	-	-
Sodium starch glycolate	-	-	-	-	-	12.5mg	-	-	-	-
Croscarmellose sodium	25mg	37.5mg	12.5mg	25mg	37.5mg	12.5mg	12.5mg	-	-	-
Crospovidone	-	-	-	-	-	-	12.5mg	12.5mg	25mg	37.5mg
Polyvinyl Pyrolidone K-30	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg
Magnesium stearate	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg
Talc	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg	2.5mg
Mannitol (Q S up to 250 mg)	126mg	100mg	100mg	75mg	50mg	75mg	75mg	150mg	125mg	100mg

Table 12: PREFORMULATION STUDIES FOR FAST DISSOLVING TABLET FORMULATION

F-Code	Angle of repose	Bulk Density	Tapped Density	% of Compressibility	Hausner ratio
F-1	24.54 ± 1.84	1.23 ± 0.02	1.45 ± 0.02	14.87 ± 2.85	1.174 ± 0.03
F-2	25.68 ± 1.66	1.25 ±0	1.48 ± 0.02	17.51 ± 0.26	1.19 ± 0.02
F-3	23.09 ± 0.22	1.19 ± 0.01	1.39 ± 0.02	14.08 ± 1.96	1.15 ± 0.03
F-4	24.15 ± 2.30	1.22 ± 0.01	1.41 ± 0.02	13.02 ± 1.53	1.14 ± 0.02
F-5	20.95 ± 0.94	1.17 ± 0.01	1.36 ± 0.01	13.96 ± 0.17	1.15 ± 0.05
F-6	28.64 ± 0.43	1.23 ± 0.02	1.45 ± 0.02	14.9 ± 0.10	1.17 ±0
F-7	29.85 ± 0.71	1.22 ± 0.01	1.38 ± 0.00	11.34 ± 1.66	1.12 ± 0.02
F-8	20.95 ± 0.85	1.19 ± 0.01	1.39 ± 0.02	14.08 ± 1.96	1.16 ± 0.02
F-9	22.55 ± 3.5	1.17 ± 0.01	1.34 ± 0.05	15.21 ± 1.25	1.17 ± 0.01
F-10	29.16 ± 2.73	1.18 ± 0.01	1.36 ± 0.01	13.22 ± 1.20	1.14 ± 0.01
F-11	23.14 ± 0.60	1.19 ± 0.01	1.40 ± 0.02	15.17 ± 1.67	1.17 ± 0.02
F-12	21.64 ± 1.91	1.18 ± 0.01	1.37 ± 0.01	13.85 ± 2.046	1.15 ± 0.02
F-13	20.88 ± 0.61	1.19 ± 0.01	1.40 ± 0.02	14.91 ± 1.22	1.17 ± 0.02
F-14	22.63 ± 1.23	1.18 ± 0.01	1.39 ± 0.02	15.29 ± 1.33	1.17 ± 0.02
F-15	22.39 ± 1.27	1.16 ±0	1.37 ± 0.01	15.31 ± 1.07	1.17 ± 0.01
F-16	21.94 ± 0.53	1.18 ± 0.01	1.38 ±0.00	14.48 ± 1.25	1.16 ± 0.01
F-17	21.25 ± 1.56	1.18 ± 0.01	1.37 ± 0.01	13.86 ± 0.17	1.15 ± 0.01
F-18	23.78 ± 1.46	1.21 ± 0.03	1.40 ± 0.02	13.50 ± 1.42	1.15 ± 0.02
F-19	21.70 ± 1.67	1.18 ± 0.01	1.40 ± 0.02	15.80 ± 0.14	1.18 ± 0.00
F-20	22.39 ± 0.20	1.17 ± 0.01	1.38 ± 0.00	14.97 ± 1.10	1.17 ± 0.01

Table 13: POST COMPRESSION EVALUATION STUDY FOR ORMELOXIFENE FAST DISSOLVING TABLET FORMULATIONS

F-Code	Weight uniformity test ± SD	DC(mg) ± SD	Hardness [kg/cm2]	Thickness (mm)	Friability [%]
F -1	244.35 ± 3.34	29.73 ± 0.17	4	3.7	0.61
F -2	243.62 ± 4.52	29.4 ± 0.45	4	3.6	0.7
F -3	248.49 ± 3.30	29.41 ± 0.12	4	3.7	0.68
F -4	248 ±4. 22	29.89 ± 0.82	4	3.7	0.69
F -5	246.04 ± 3.73	29.20 ± 0.35	4	3.7	0.72
F -6	248.11 ± 2.89	29.47± 0.30	4	3.7	0.67
F -7	247.32 ± 1.9	29.32 ± 0.34	4	3.7	0.63
F -8	248.76 ± 2.09	29.33 ± 0.34	4	3.7	0.71
F -9	247.98 ± 2.39	29.39 ± 0.17	4	3.7	0.7
F -10	247.6 ± 2.69	29.81 ± 0.47	4	3.7	0.56
F -11	247.1 ± 1.73	29.47 ± 0.21	4	3.7	0.67
F -12	146.35 ± 1.2	29.37 ± 0.34	4	3.5	0.66
F -13	246.98 ± 1.38	29.40 ± 0.17	4	3.5	0.56
F -14	248.3 ± 1.28	29.66 ± 0.43	4	3.5	0.7
F -15	246.69 ± 1.42	29.19 ± 0.27	4	3.7	0.63
F -16	246.93 ± 1.02	29.12 ± 0.11	4	3.6	0.69
F -17	247.17 ± 1.28	29.10 ± 0.27	4	3.6	0.63
F -18	247.14 ± 0.99	29.31 ± 0.34	4	3.7	0.69
F -19	247.45 ± 0.95	29.37 ± 0.30	4	3.7	0.6
F -20	245.7 ± 2.79	29.22 ± 0.34	4	3.7	0.69

Table 14: POST COMPRESSION EVALUATION STUDY FOR ORMELOXIFENE FAST DISSOLVING TABLET FORMULATIONS

F- code	Disintegration Time [Sec]	Water Ab. Ratio (%)	Wetting Time [Sec]
F -1	166.33 ±1.52	9.87 ±1.17	228.33 ±2.08
F -2	145.66 ±2.08	18.20 ±1.33	178.33 ±1.52
F -3	88.33 ±1.52	45.25 ±2.04	116.33 ±1.52
F -4	129.66 ±2.08	21.08 ±1.72	153.33 ±2.51
F -5	86.33 ±1.52	40.37 ±1.11	126.33 ±1.15
F -6	72.33 ±2.08	57.61 ±1.34	62.66 ±1.52
F -7	155.66 ±1.52	13.34 ±0.05	181.66 ±1.52
F -8	58.33 ±1.52	73.75 ±2.27	53.66 ±1.52
F -9	70.33 ±2.51	71.59 ±2.66	59.66 ±1.52
F -10	137.66 ±1.52	12.57 ±1.34	159.66 ±1.52
F -11	148.33 ±1.52	20.80 ±0.28	162.66 ±1.52
F -12	127.66 ±1.52	19.28 ±0.76	147.66 ±1.52
F -13	123.33 ±1.52	27.82 ±1.39	141.66 ±1.52
F -14	87.66 ±1.52	49.27 ±0.42	134.66 ±0.57
F -15	86.33 ±2.08	72.94 ±1.97	120.66 ±081
F -16	143.66 ±1.52	26.36 ±0.23	152.33 ±1.15
F -17	126.33 ±1.15	26.93 ±0.25	131.66 ±0.57
F -18	146.33 ±2.08	22.68 ±0.38	155.66 ±1.52
F -19	129.33 ±0.57	32.09 ±0.60	126.33 ±0.57
F -20	87.33 ±2.081	52.00 ±0.13	99.33 ±2.30

Table 15: SOLUBILITY STUDY

Medium	Pure drug [mg/ml]	Solid dispersion [mg/ml]	Fast dissolving tablet [mg/ml]
Distilled water	0.266 ± 0.01	0.556 ± 0.01	0.79 ± 0.01
pH 6.8 buffer	0.3 ± 0.01	0.603 ± 0.01	0.81 ± 0.02

Table 16: STABILITY STUDY

Parameter	Initial	After 10 days	After 20 days	After 30 days	After 45 days
Physical appearance	Pale white	Pale white	Pale white	Pale white	Pale white
Hardness[kg/cm^2]	4	4	4.5	4.5	4.8
Water absorption ratio [%]	73.75	73.75	73.75	73.75	73.50
Wetting time [seconds]	53	53	56	56	58
Disintegration time [Sec]	58	58	59	59	60
Drug content [%]	97.76	97	97	96.33	96.33
Drug release profile [%]	95	94.96	94.55	94.14	94.10

FIGURE 1: DETERMINATION OF λ max OF ORMELOXIFENE HYDROCHLORIDE

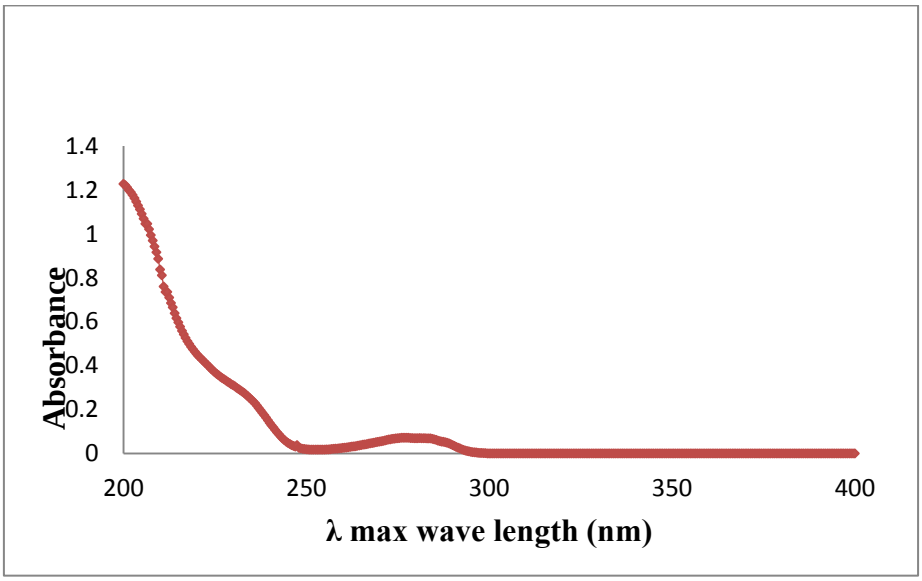


FIGURE 2(a): CALIBRATION OF ORMELOXIFENE HCL WITH DISTILLED WATER

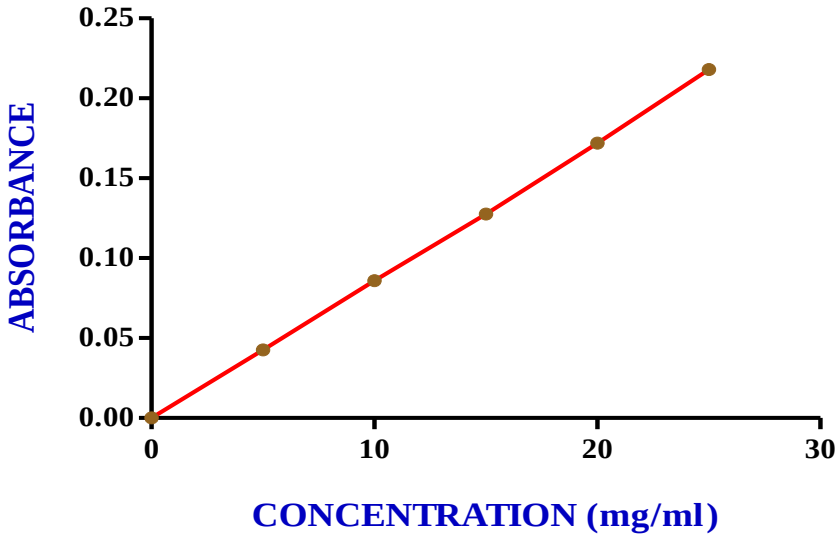


FIGURE 2(b) CALIBRATION OF ORMELOXIFENE.HCL WITH pH 6.8 BUFFER

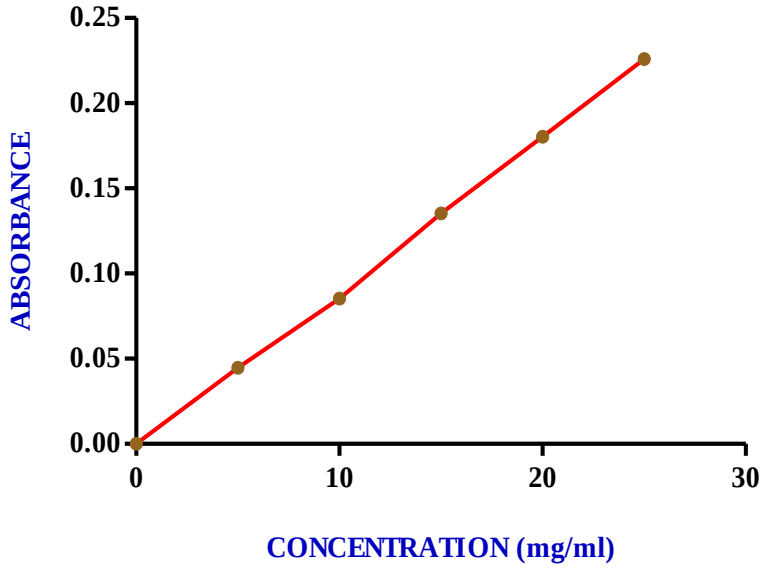


FIGURE 3: INVITRO RELEASE STUDY OF ORMELOXIFENE PURE DRUG

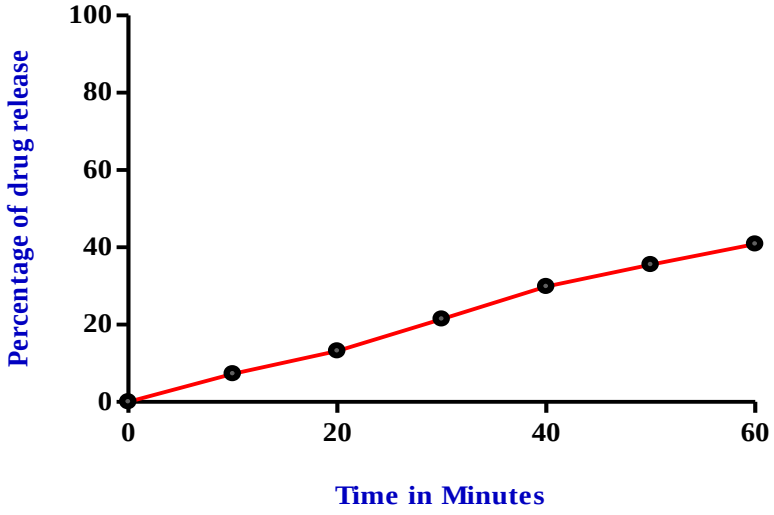


FIGURE 4: DISSOLUTION STUDY OF ORMELOXIFENE SOLID DISPERSION BY KNEADING METHOD

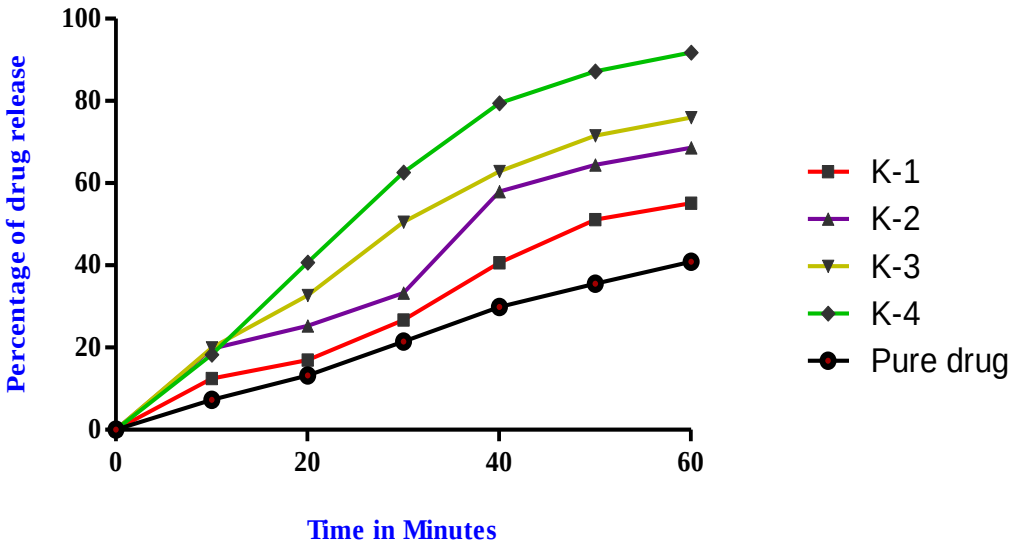


FIGURE 5: DISSOLUTION STUDY OF ORMELOXIFENE SOLID DISPERSION BY MELTING METHOD

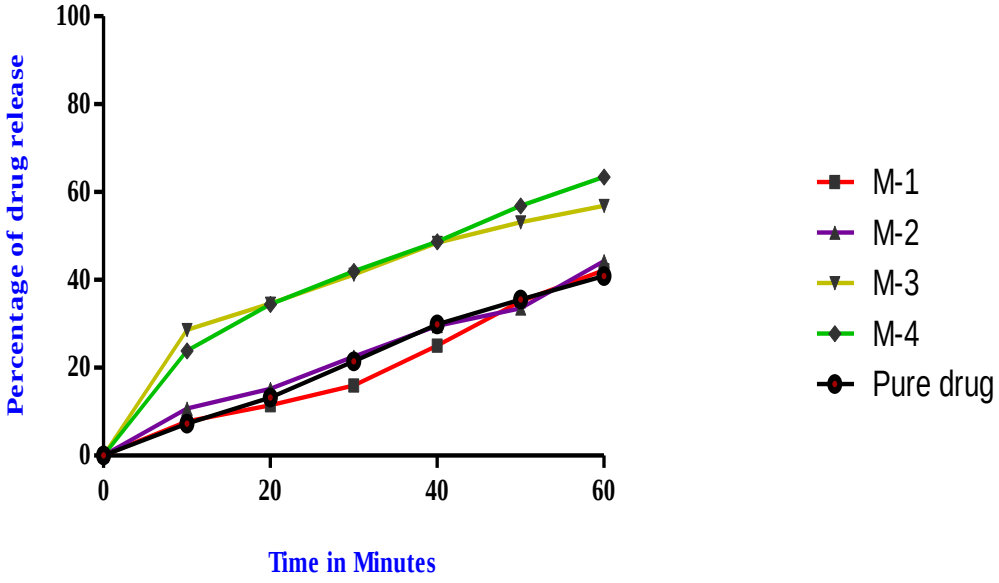


FIGURE 6: DISSOLUTION STUDY OF ORMELOXIFENE SOLID DISPERSION PRODUCT BY COPRECIPITATION METHOD

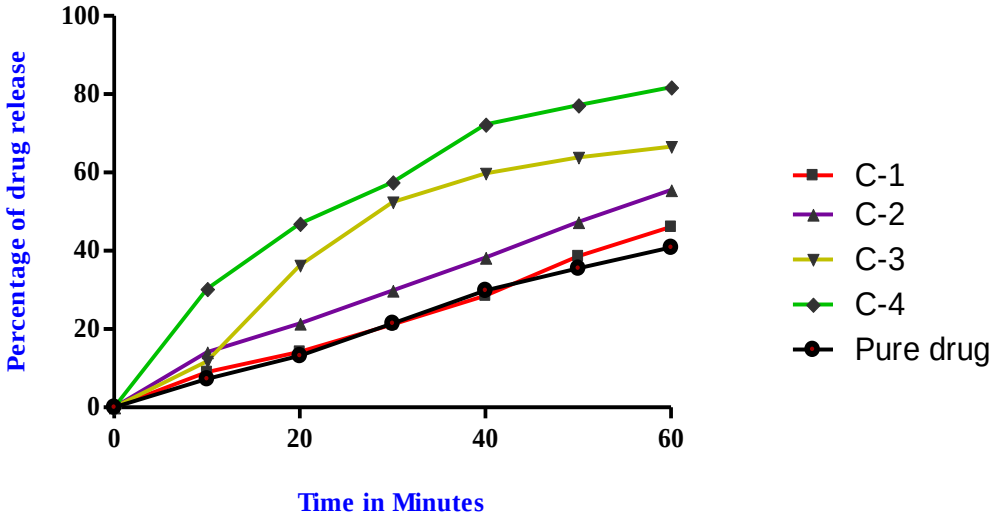


FIGURE 7: DISSOLUTION STUDY OF ORMELOXIFENE SOLID DISPERSION PRODUCT BY SOLVENT EVAPORATION METHOD

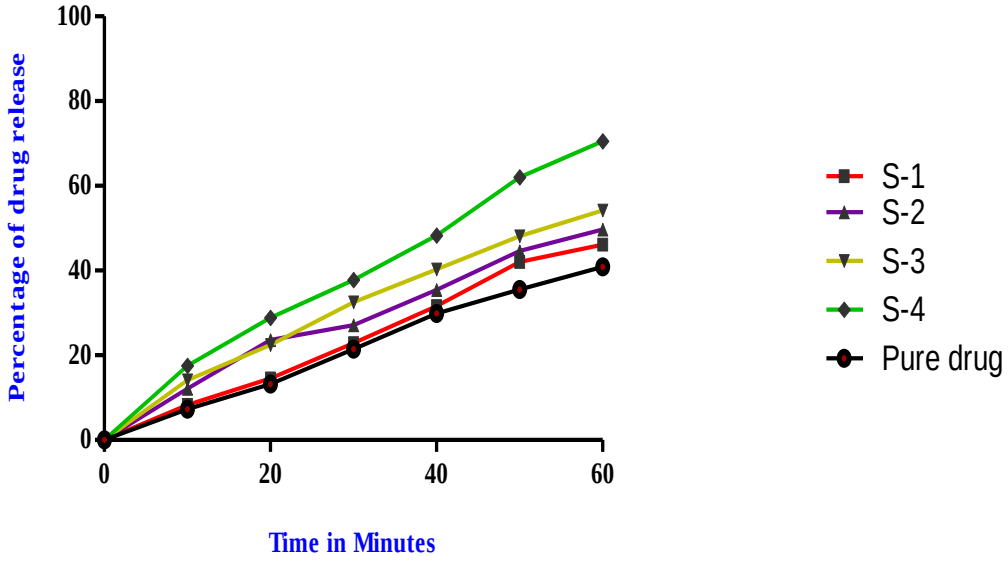


FIGURE 8: COMPARISION OF INVITRO RELEASE PROFILE OF SOLID DISPERSION WITH DIFFERENT CARRIERS IN 1:1 RATIO

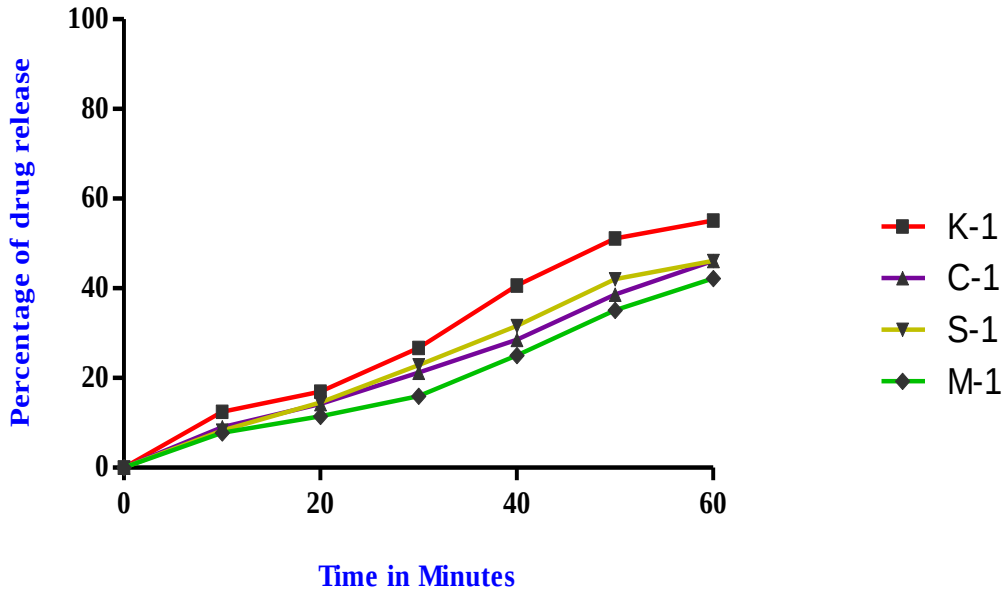


FIGURE 9: COMPARISION OF INVITRO RELEASE PROFILE OF SOLID DISPERSION WITH DIFFERENT CARRIERS IN 1:2 RATIO

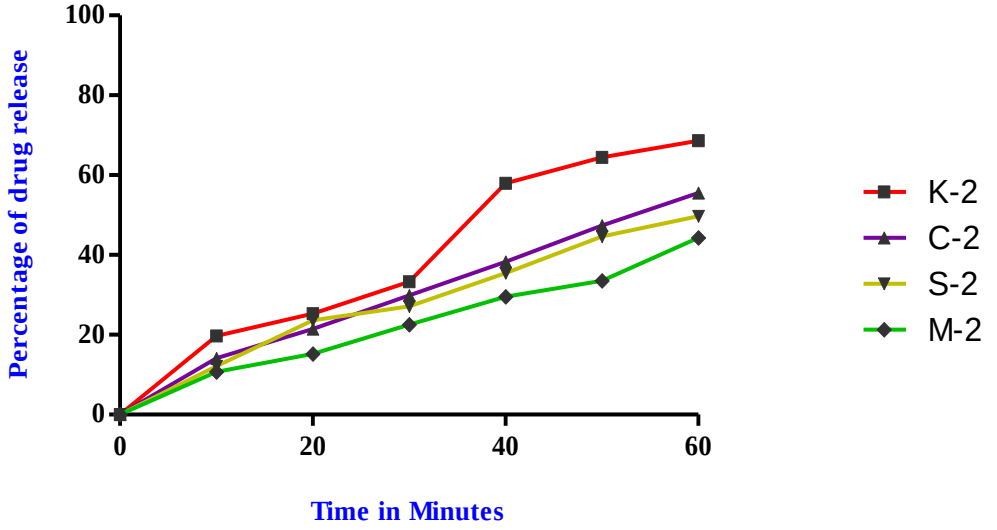


FIGURE 10: COMPARISION OF INVITRO RELEASE PROFILE OF SOLID DISPERSION WITH DIFFERENT CARRIERS IN 1:3 RATIO

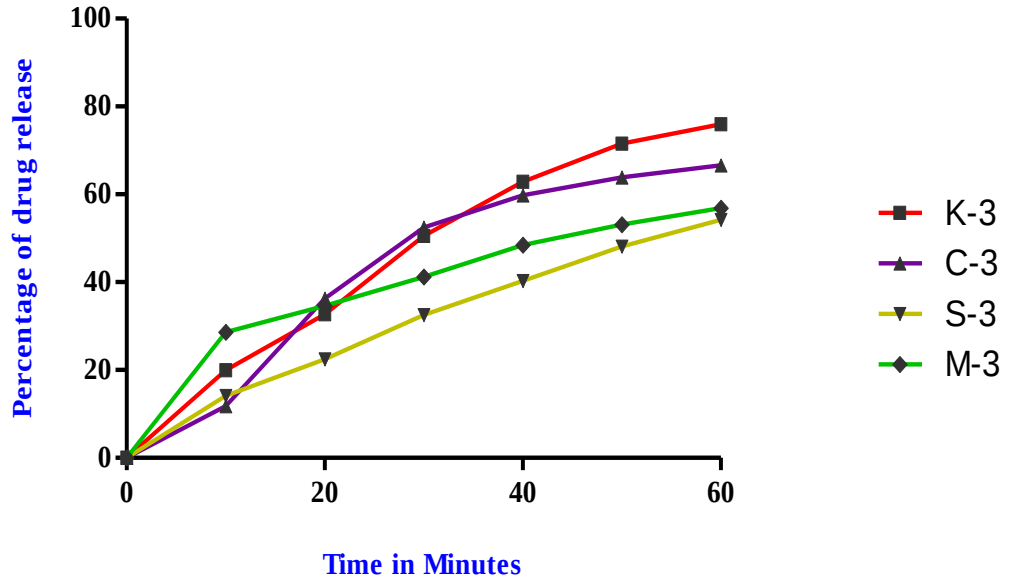


FIGURE: 11 COMPARISION OF INVITRO RELEASE PROFILE OF SOLID DISPERSION WITH DIFFERENT CARRIERS IN 1:4 RATIO

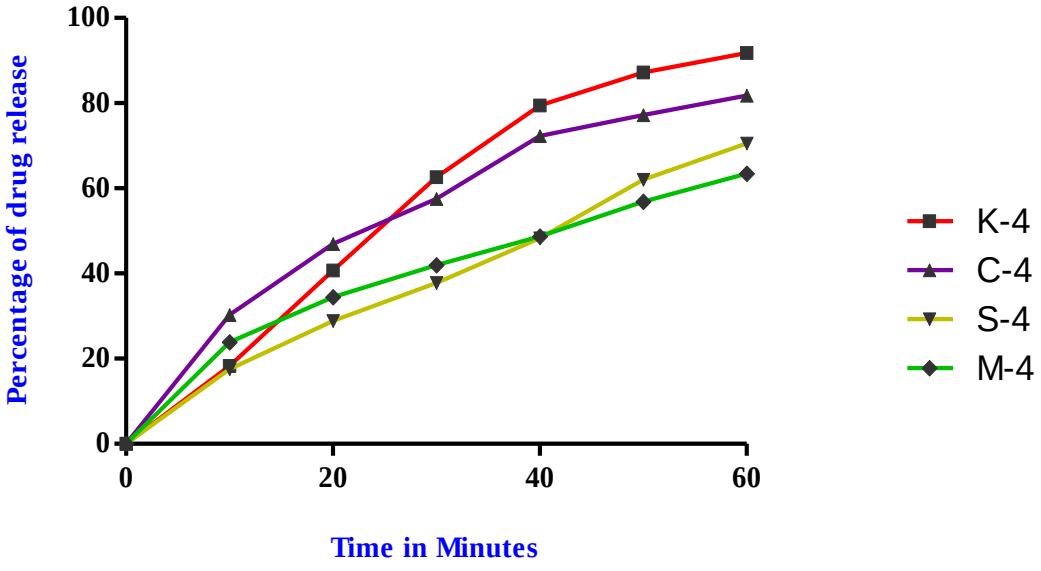


FIGURE 12: COMPARISION OF INVITRO RELEASE PROFILE OF PHYSICAL MIXTURE WITH DIFFERENT CARRIERS AND DIFFERENT RATIO

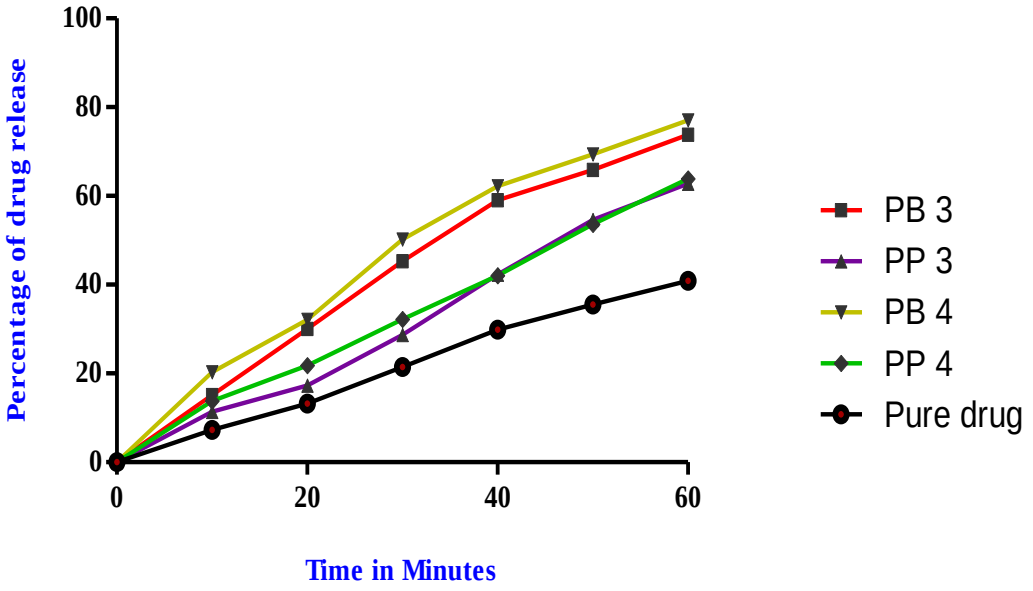


FIGURE 13: COMPARISION OF INVITRO RELEASE PROFILE OF BEST RELEASE SOLID DISPERSION IN WITH DIFFERENT CARRIERS AND DIFFERENT RATIO

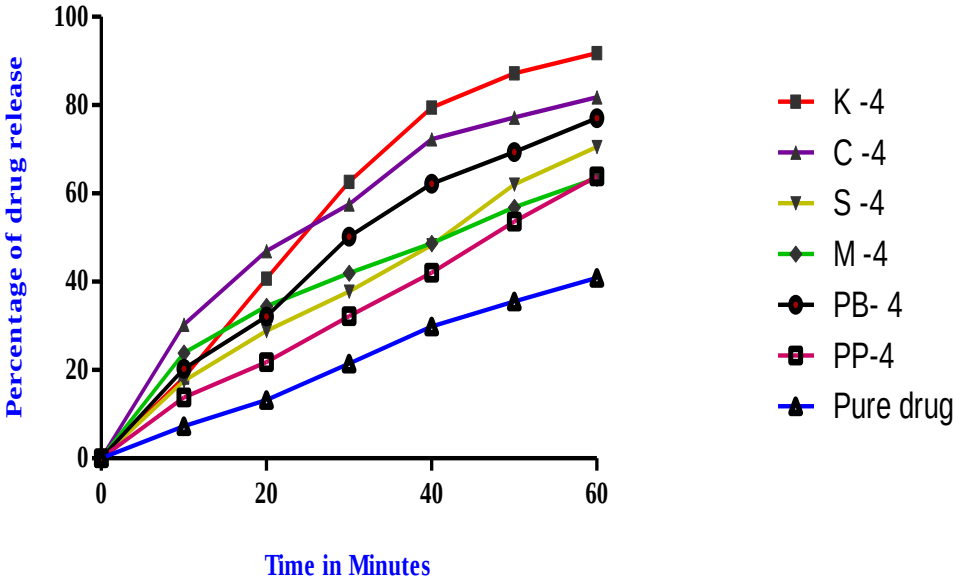


FIGURE 14: SOLUBITY STUDY

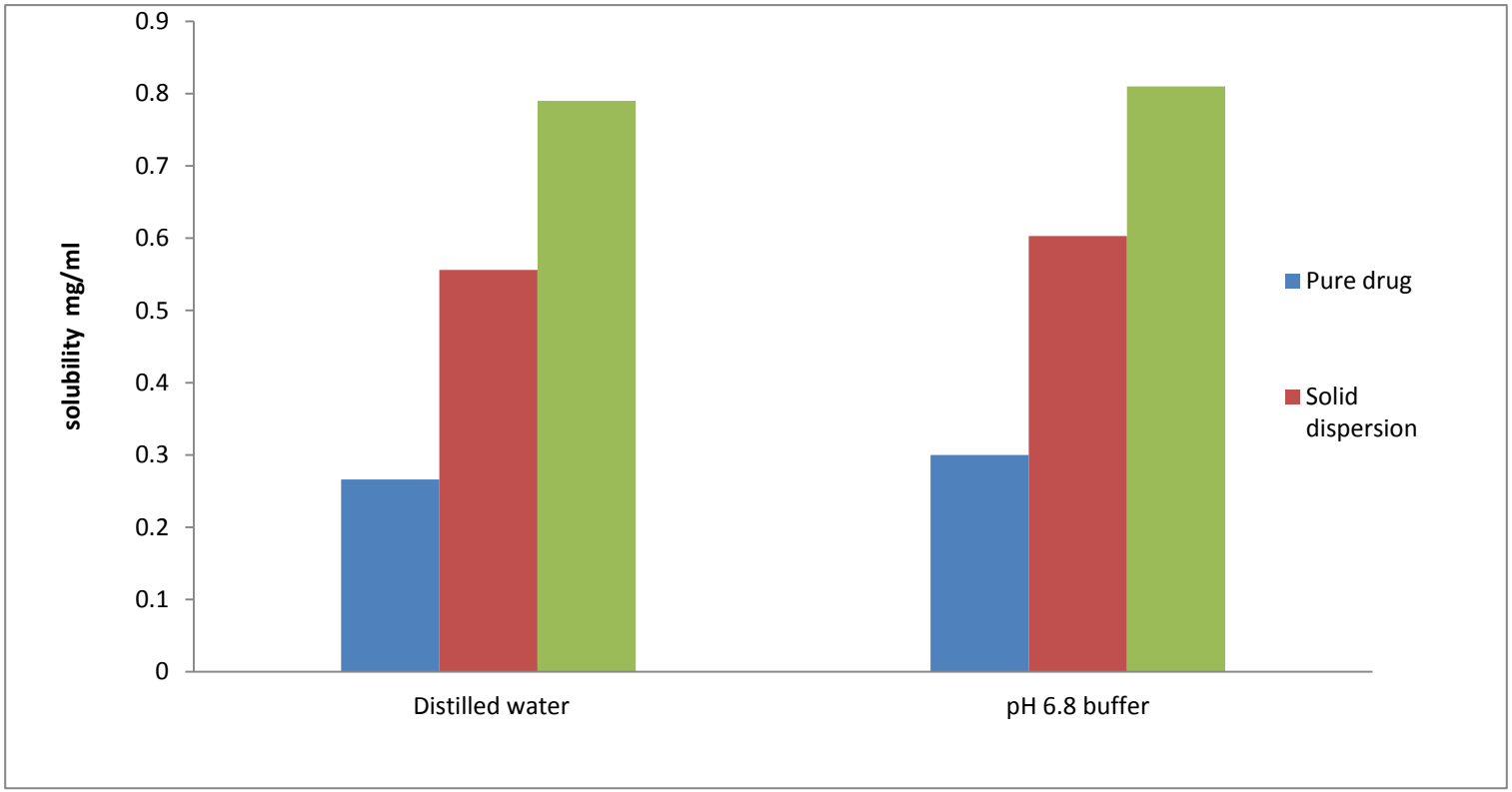


FIGURE 15: ANGLE OF REPOSE

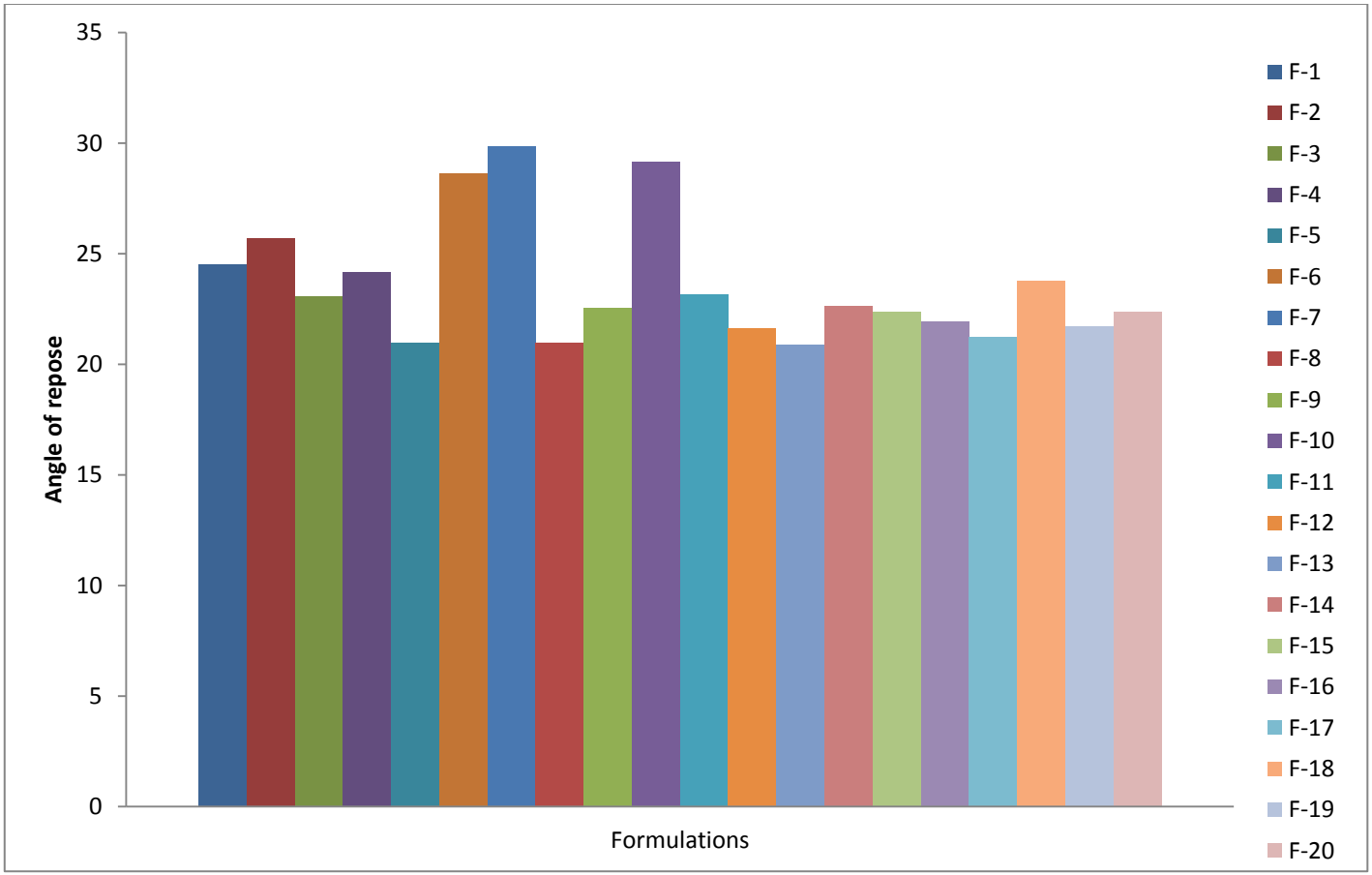


FIGURE 16: BULK DENSITY

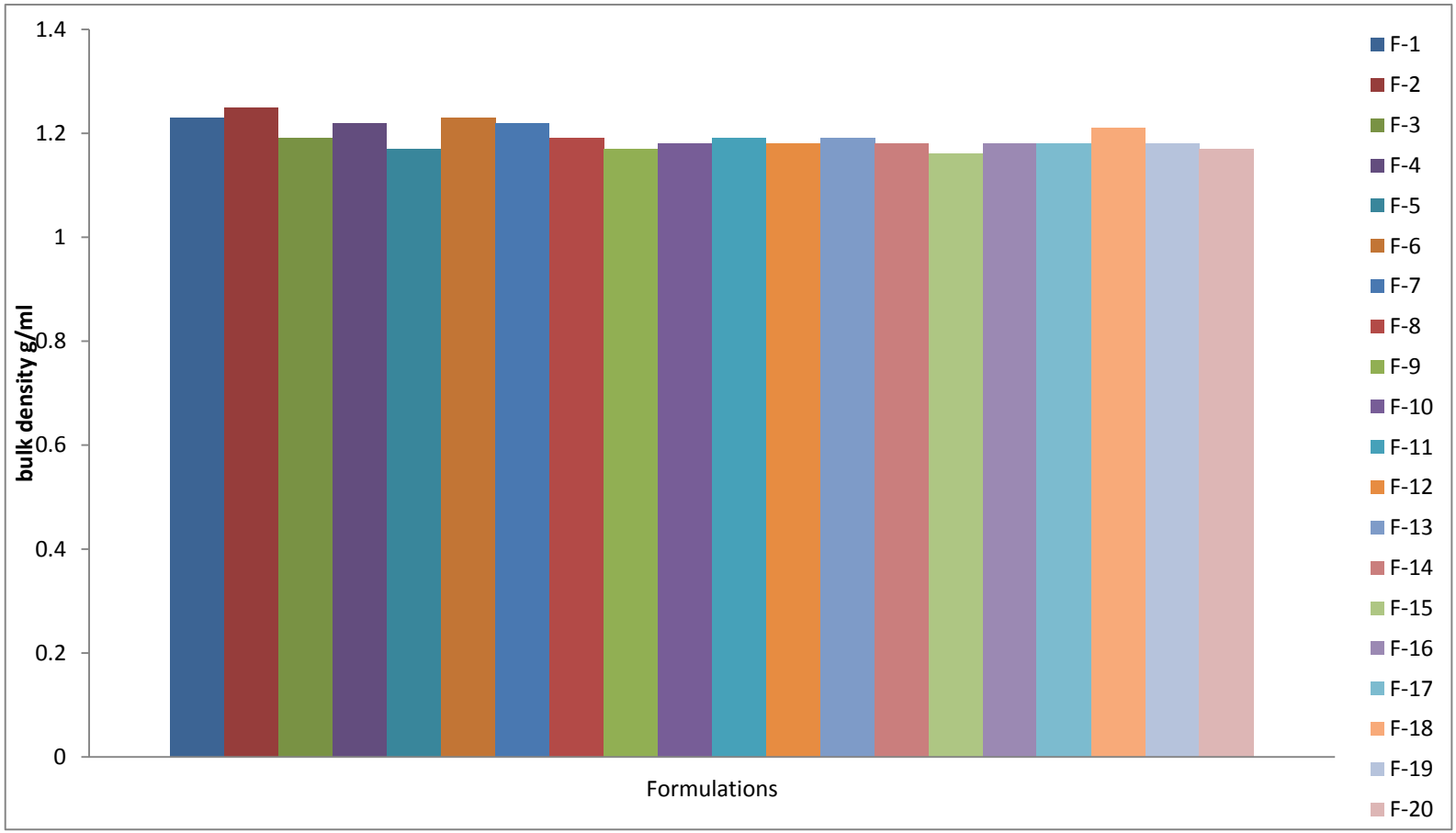


FIGURE 17: TAPPED DENSITY

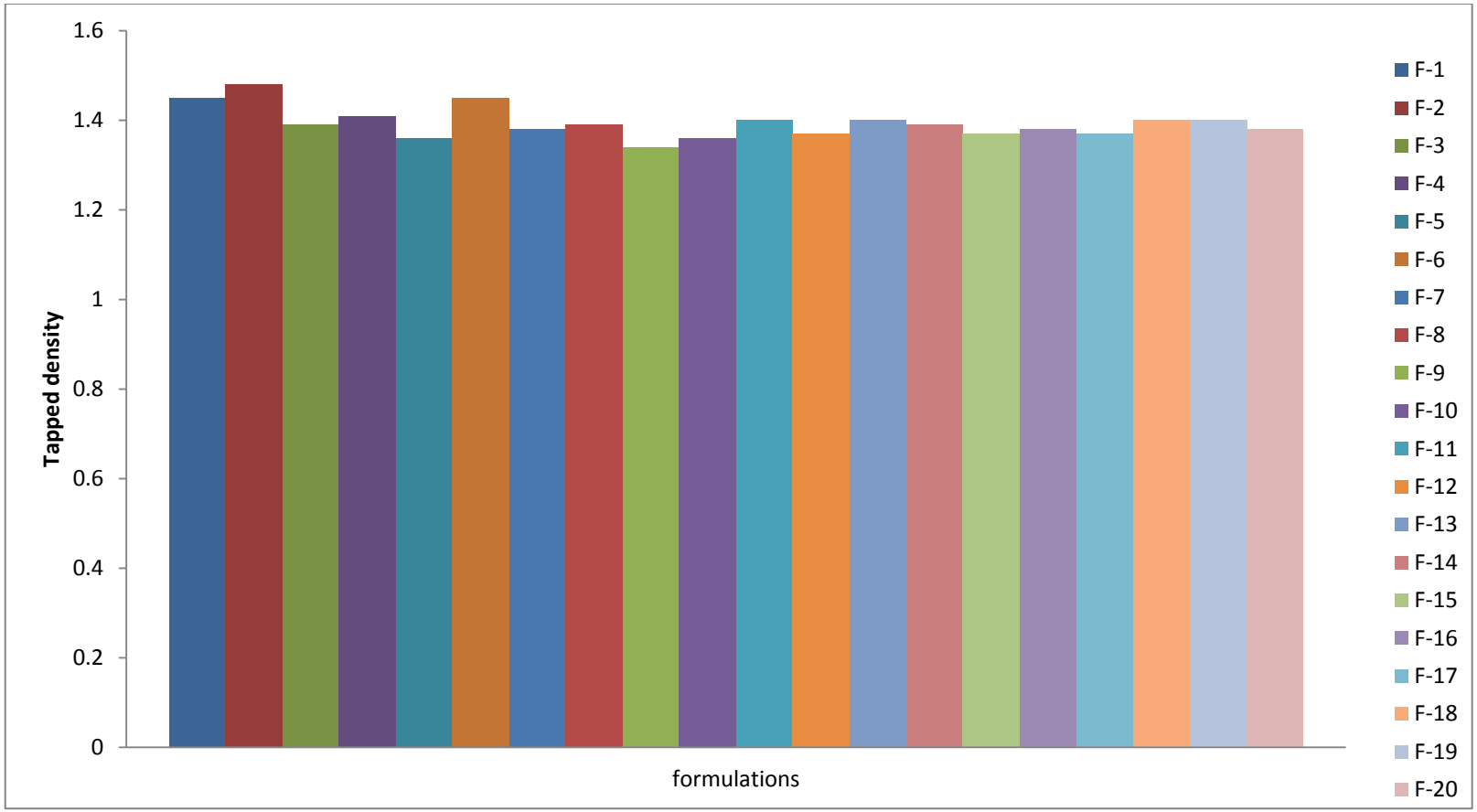


FIGURE 18: CARR'S COMPRESSIBILITY

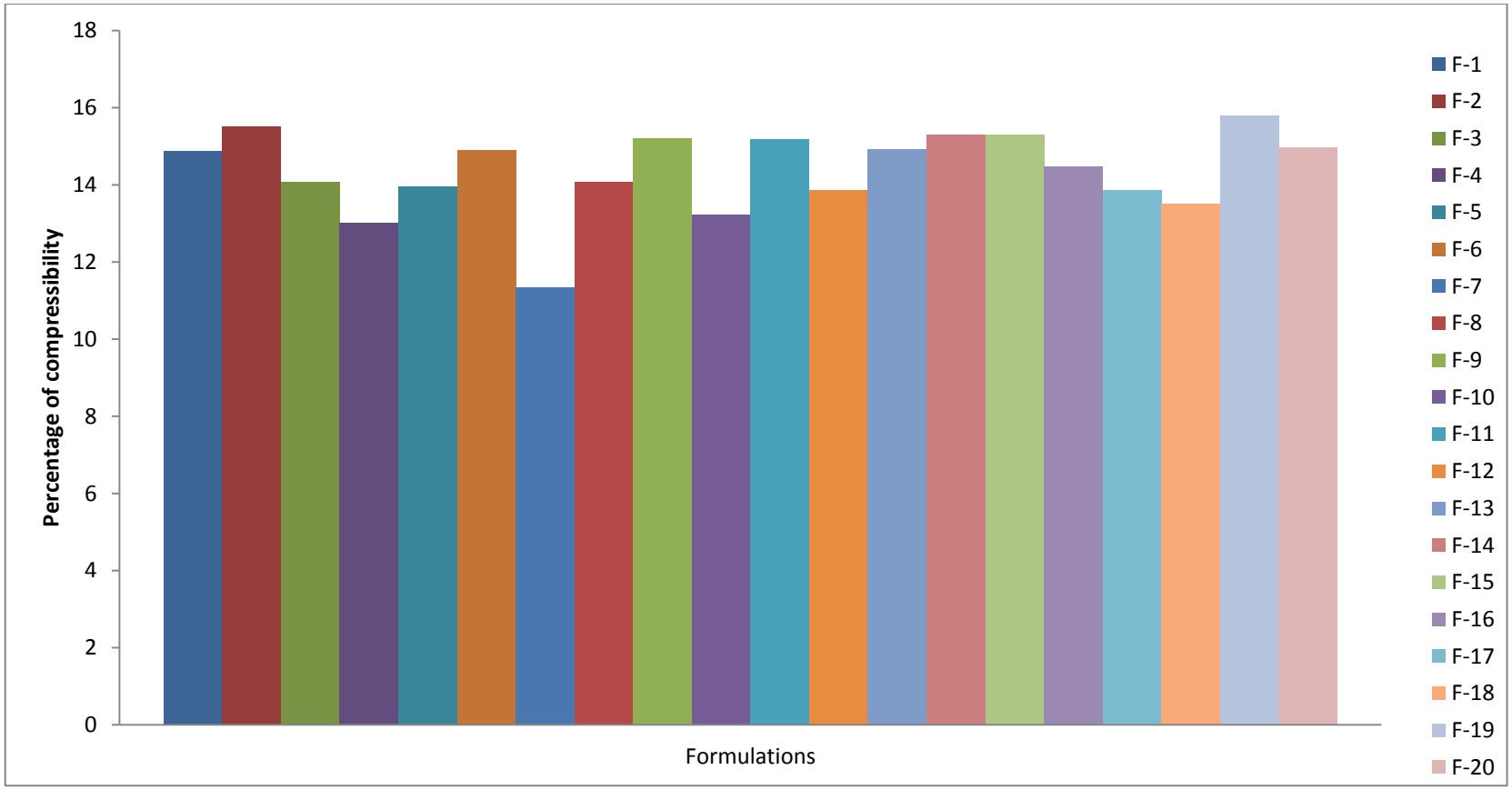


FIGURE 19: HAUSNER'S RATIO

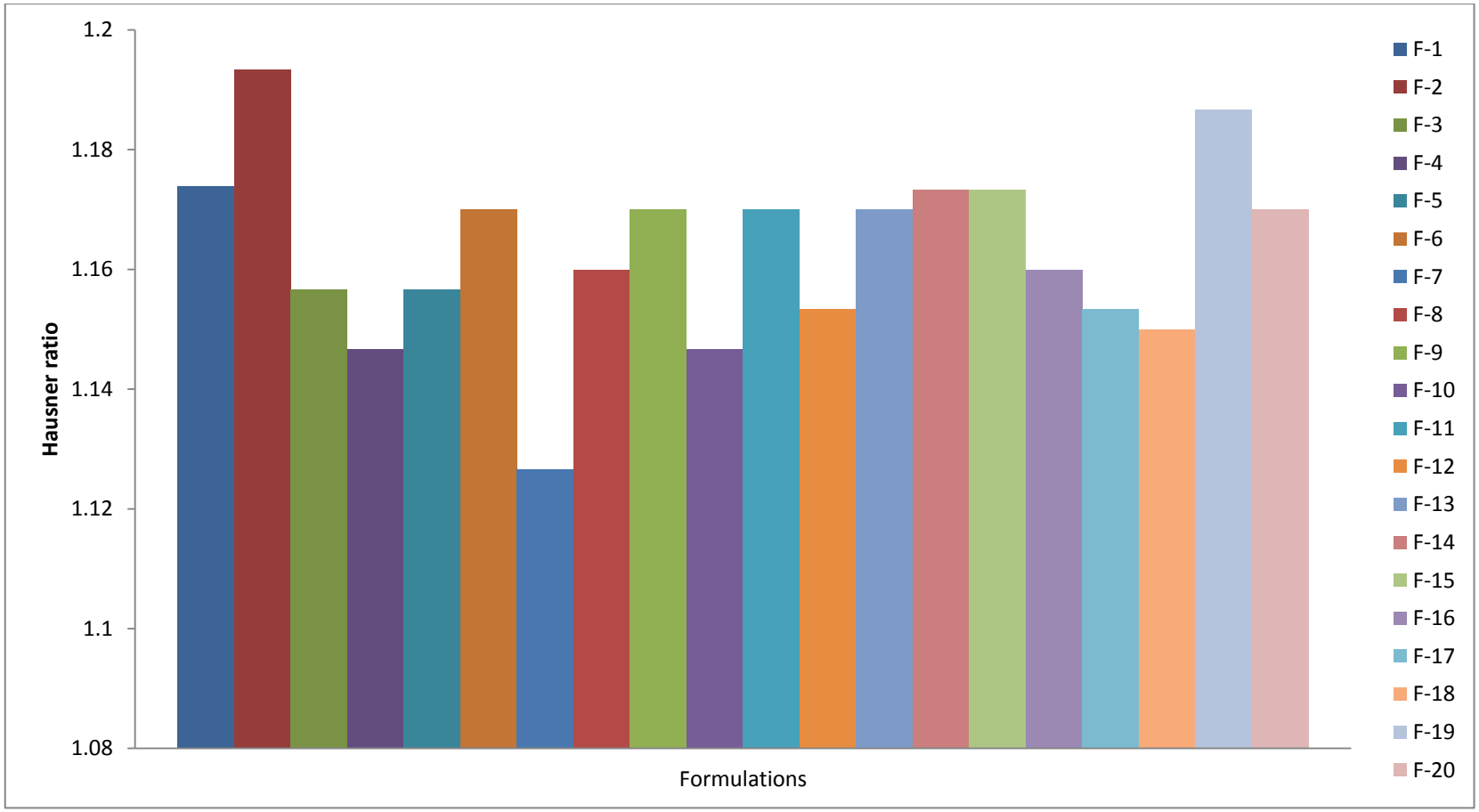


FIGURE 20: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F1 to F3)

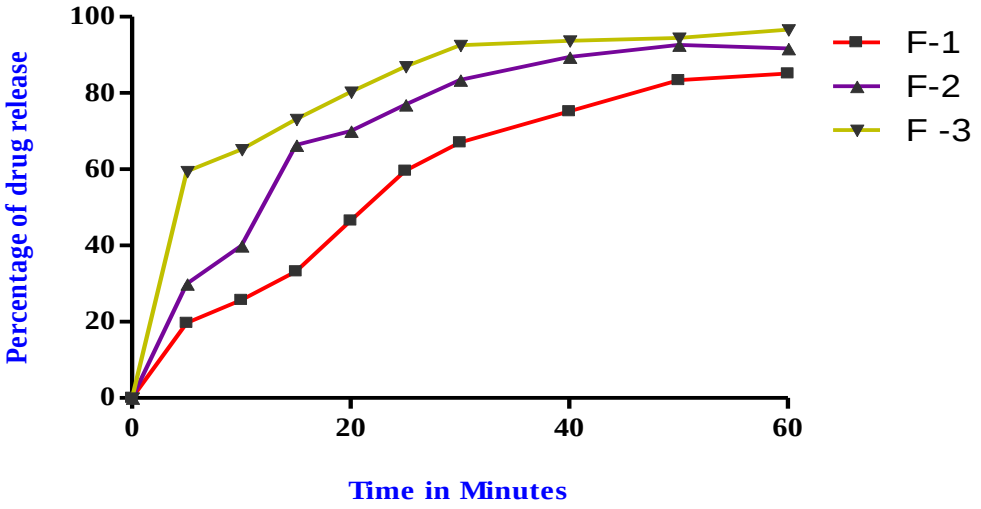


FIGURE 21: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F4 to F6)

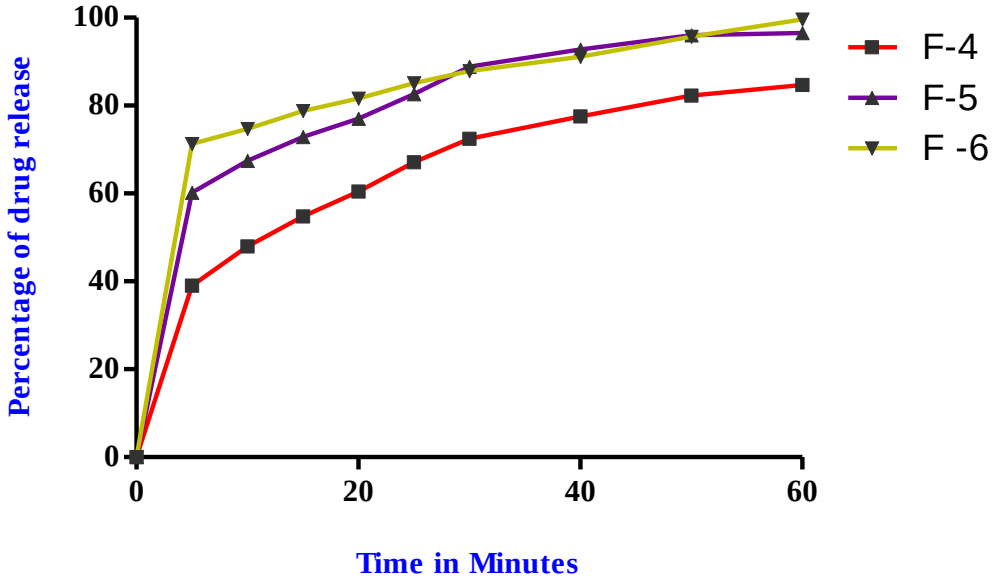


FIGURE 22: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F7 to F9)

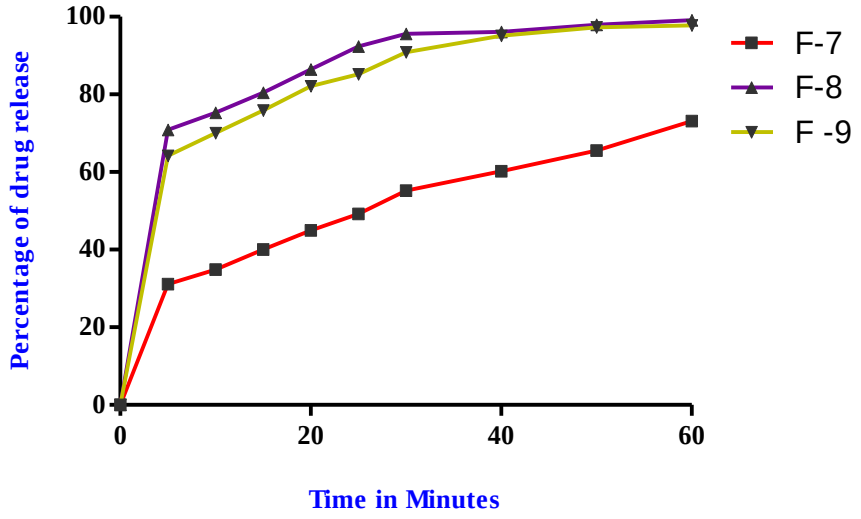


FIGURE 23: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F10 to F12)

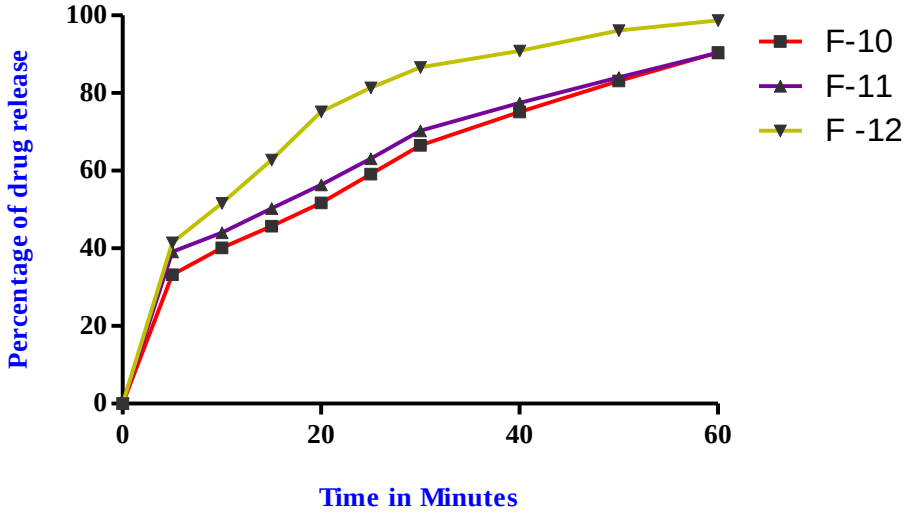


FIGURE 24: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F13 to F15)

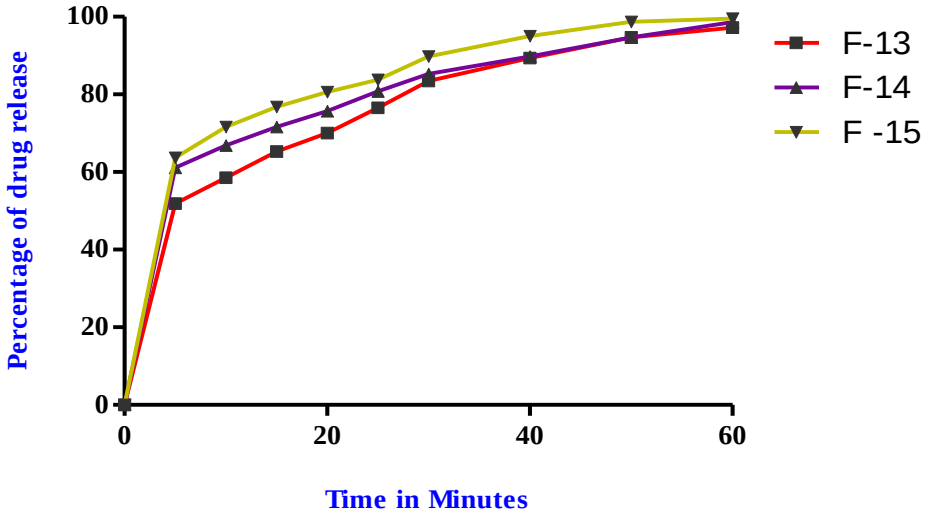


FIGURE 25: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F16 & F17)

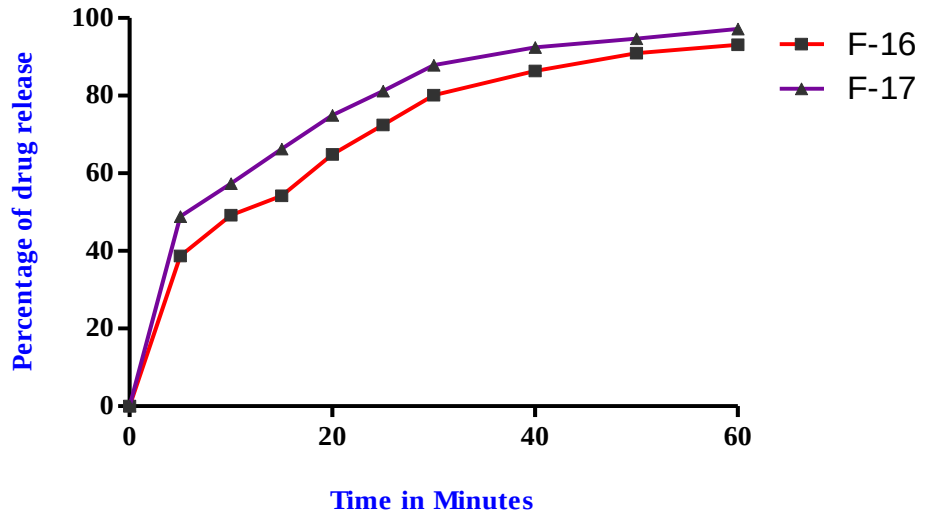


FIGURE 26: ORMELOXIFENE FAST DISSOLVING TABLET DRUG RELEASE PROFILE (F18 to F20)

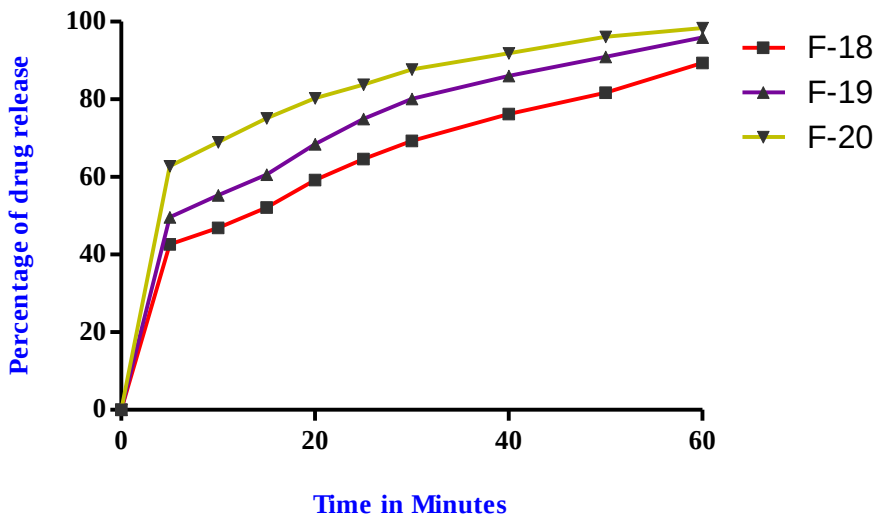


FIGURE 27 (a): FT-IR SPECTRUM OF ORMELOXIFENE

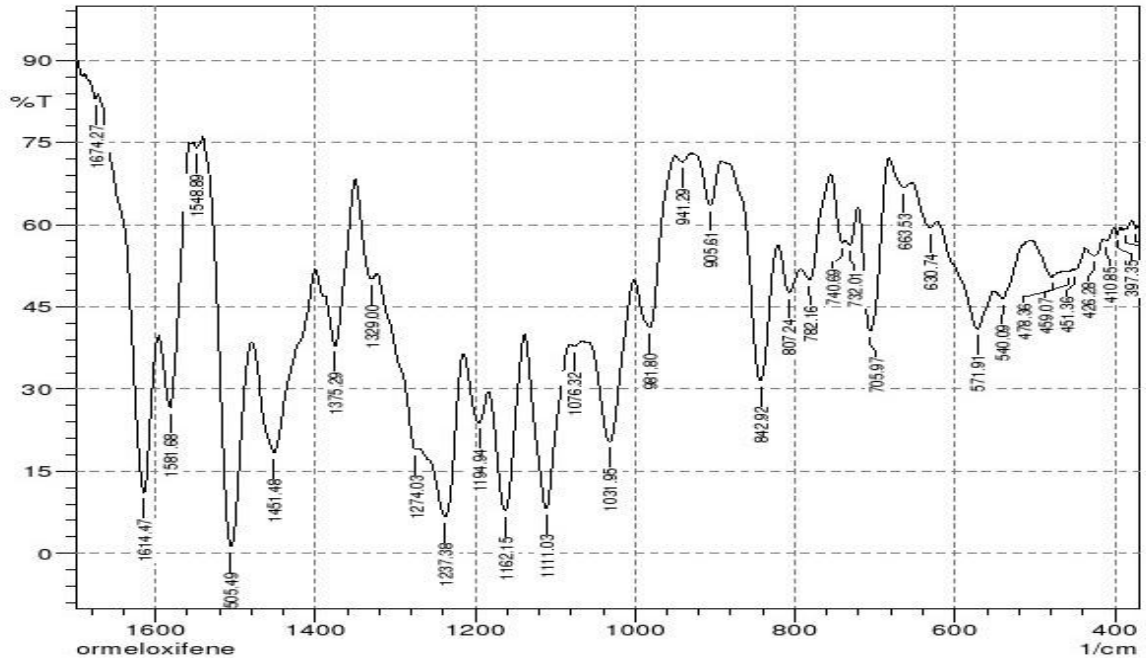


FIGURE 27 (b): FT-IR SPECTRUM OF SODIUM STARCH GLYCOLATE

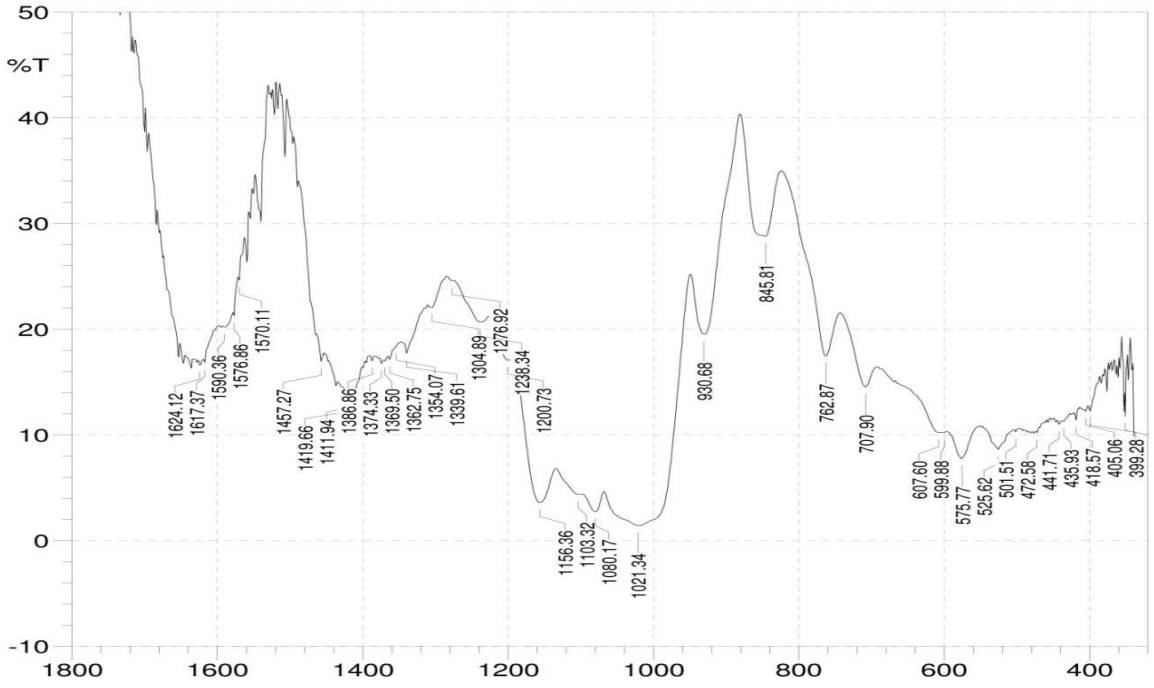


FIGURE 27 (c): FT-IR SPECTRUM OF CROSCARMELLOSE SODIUM

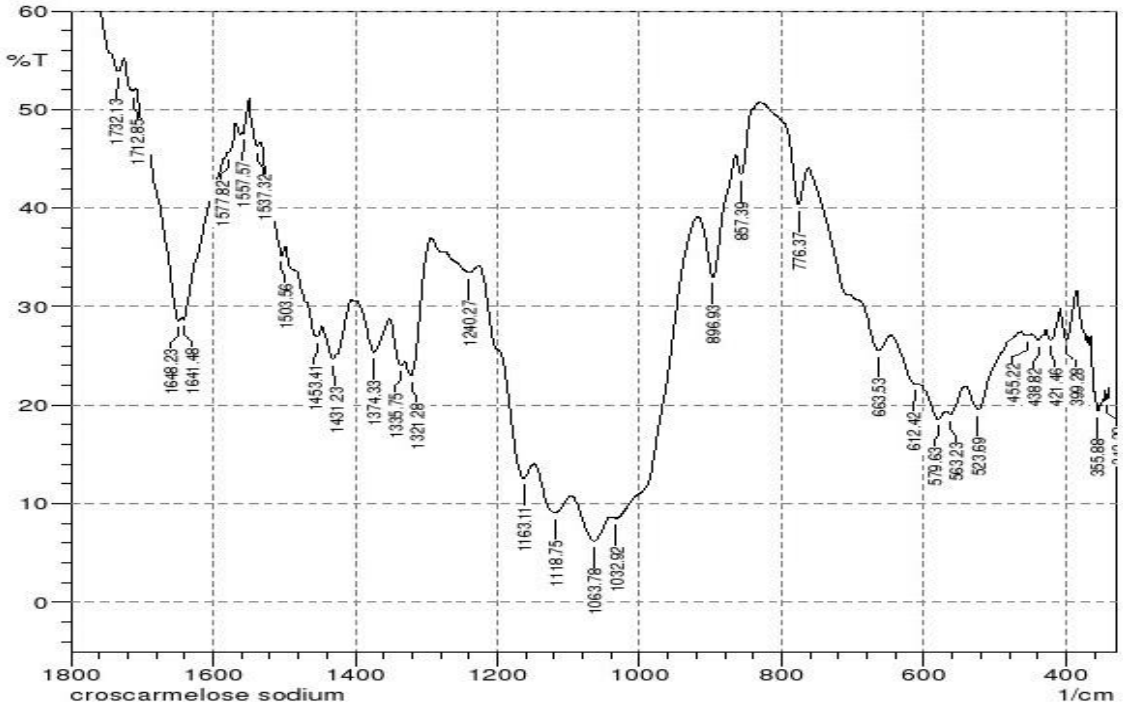


FIGURE 27 (d): FT-IR SPECTRUM OF CROSPOVIDONE

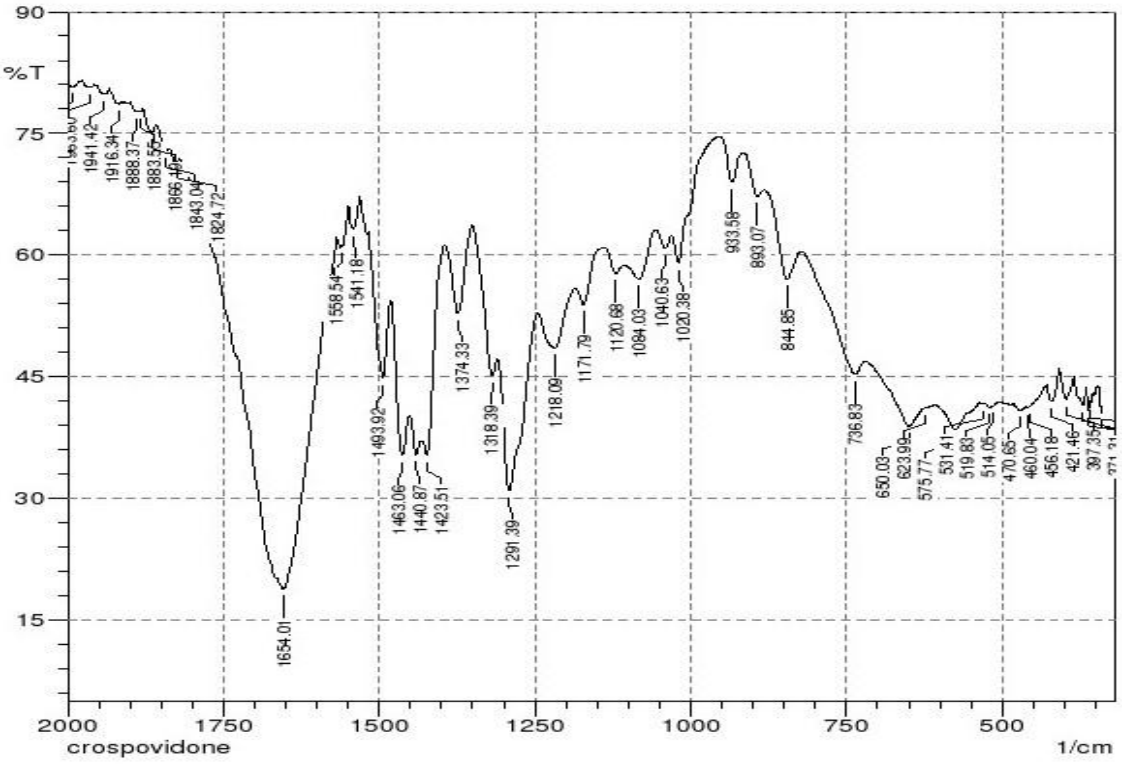


FIGURE 27 (e): FT-IR SPECTRUM OF BETACYCLODEXTRIN

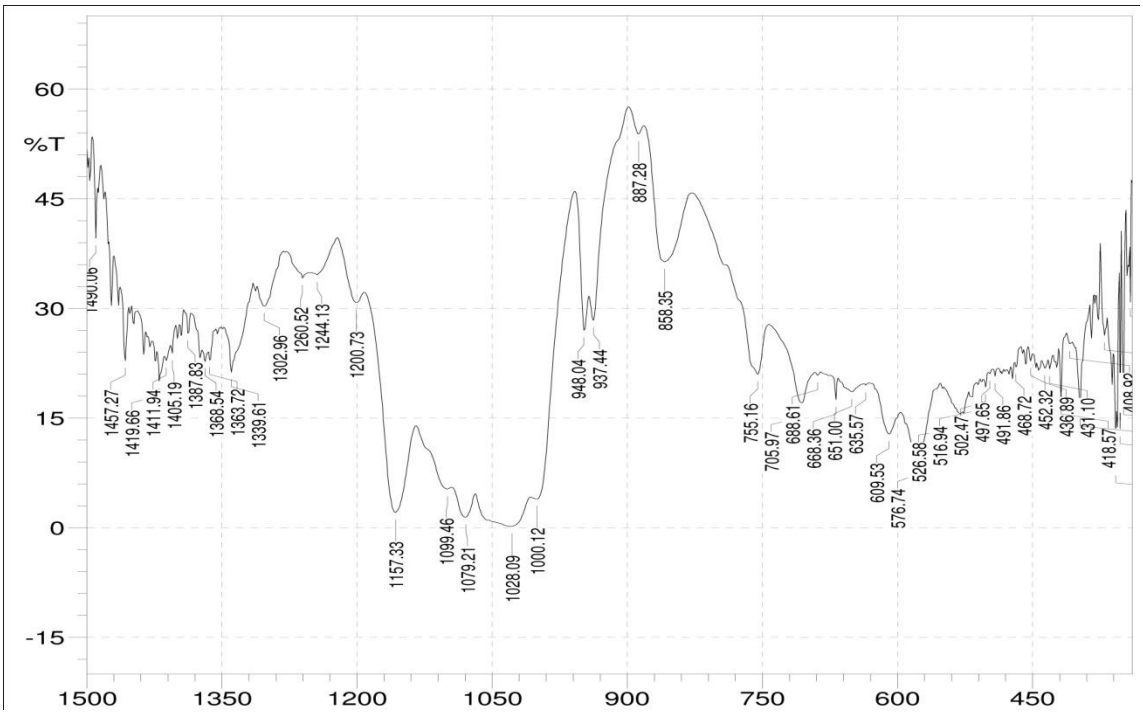


FIGURE 27 (f): FT-IR SPECTRUM OF MICROCRYSTALLINE CELLULOSE

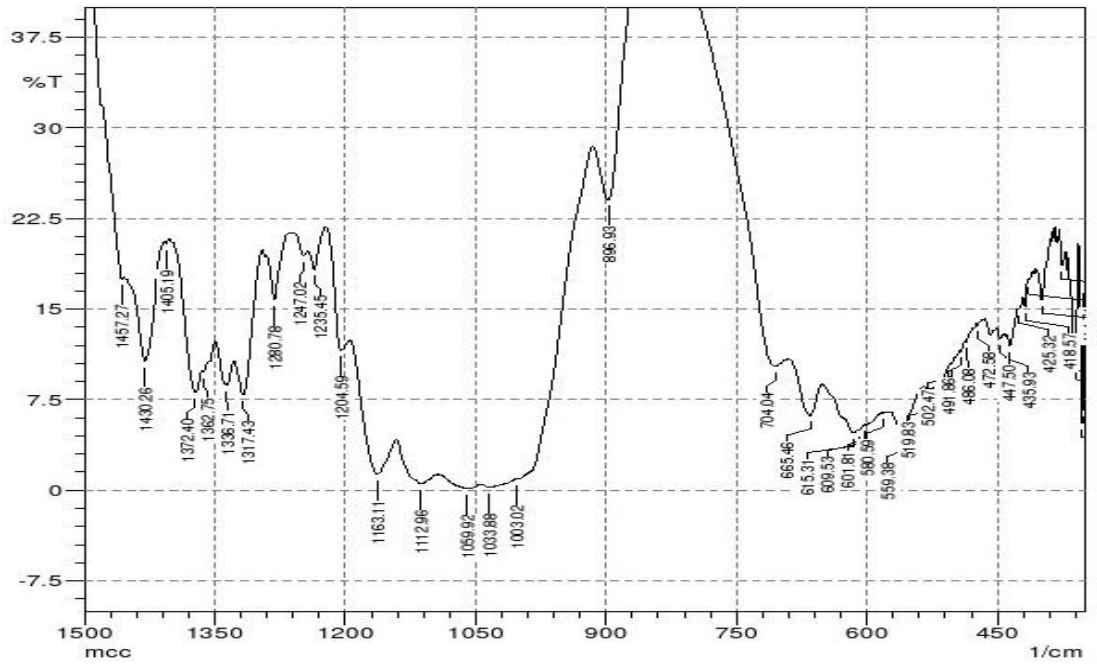


FIGURE 27 (g): FT-IR SPECTRUM OF MANNITOL

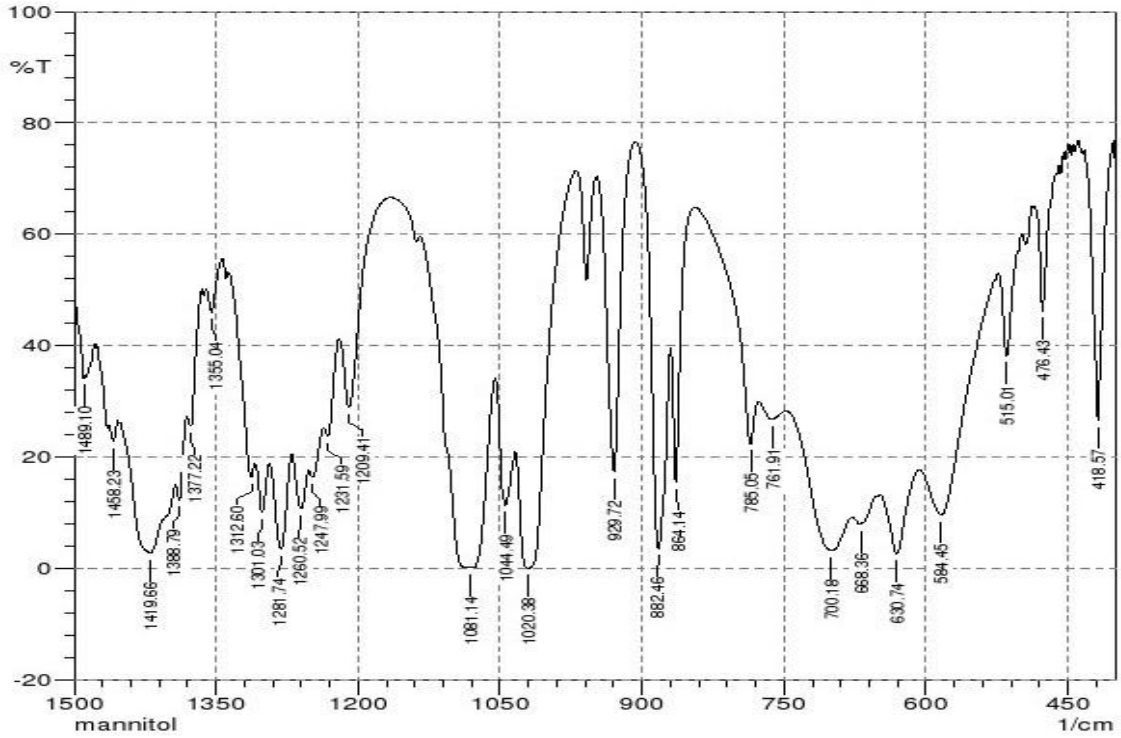


FIGURE 27 (h): FT-IR SPECTRUM OF PEG 6000

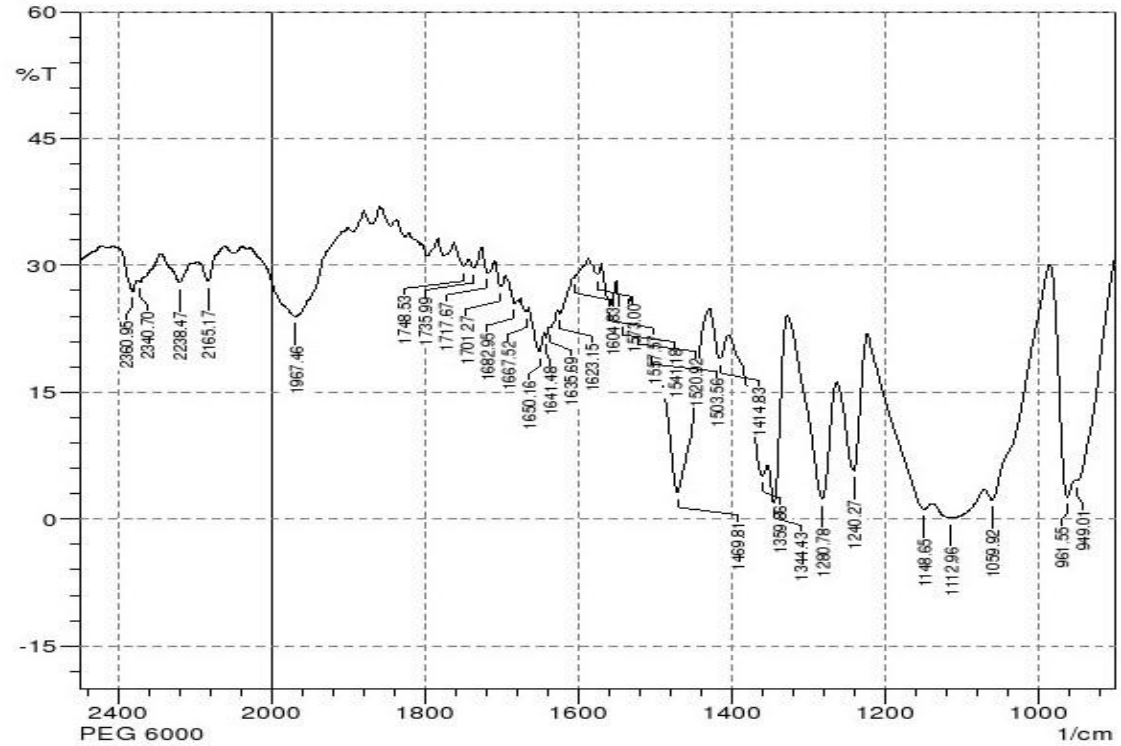


FIGURE 27 (i): FT-IR SPECTRUM OF PVP K30

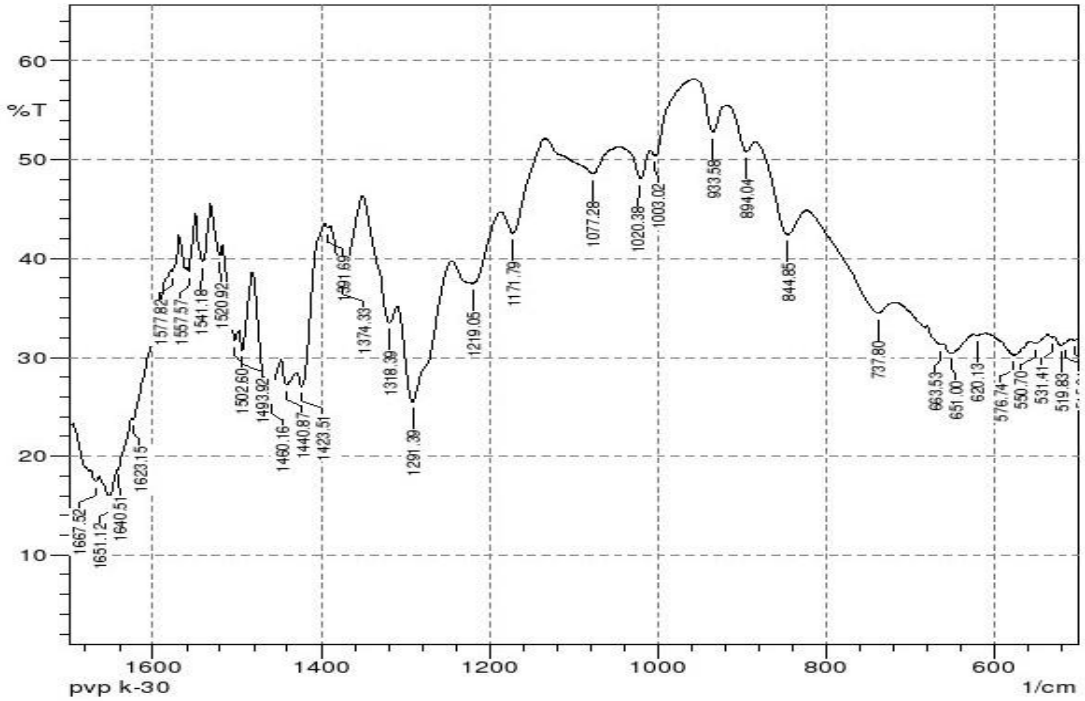


FIGURE 27 (j): FT-IR SPECTRUM OF (ORMELOXIFENE + CCS + CP+ MCC)

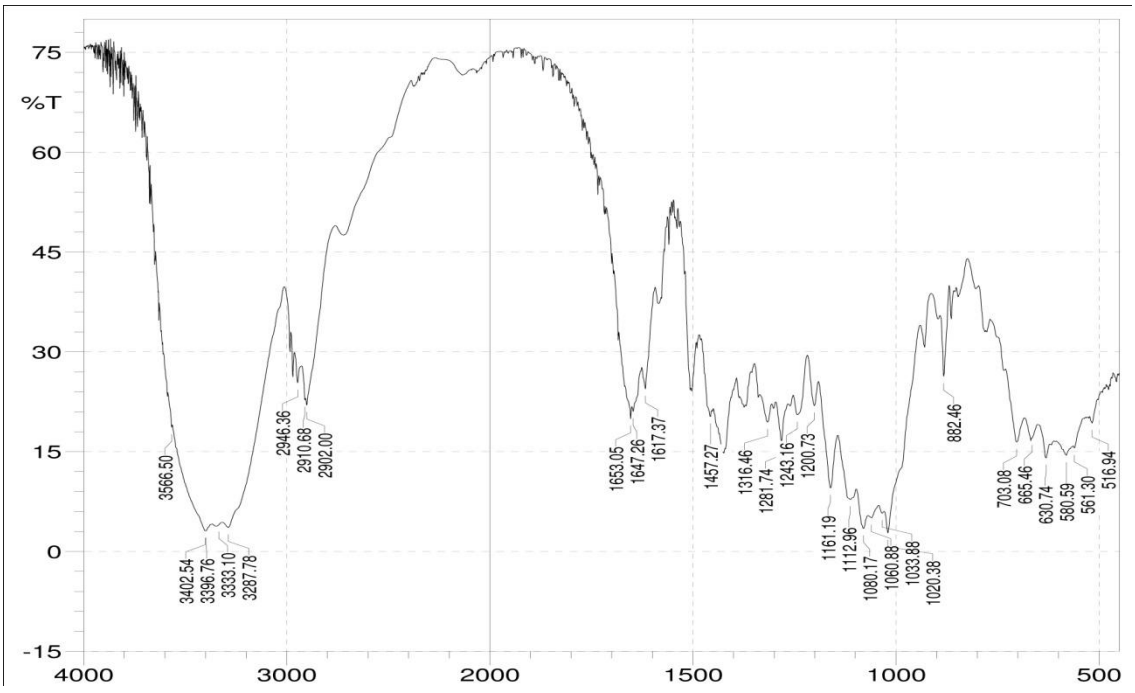


FIGURE 27 (k): FT-IR SPECTRUM OF (ORMELOXIFENE + SSG + CCS + CP+ MCC)

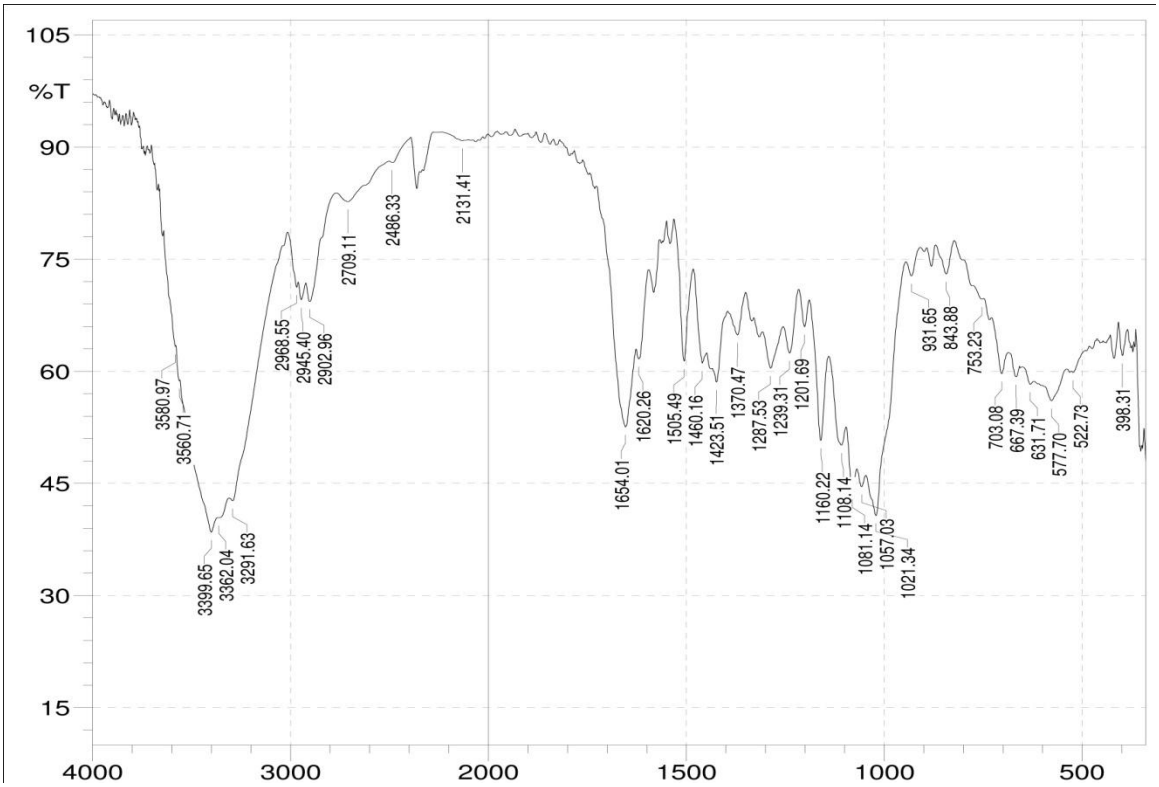


FIGURE 27 (l): FT-IR SPECTRUM OF (ORMELOXIFENE + CCS + MCC)

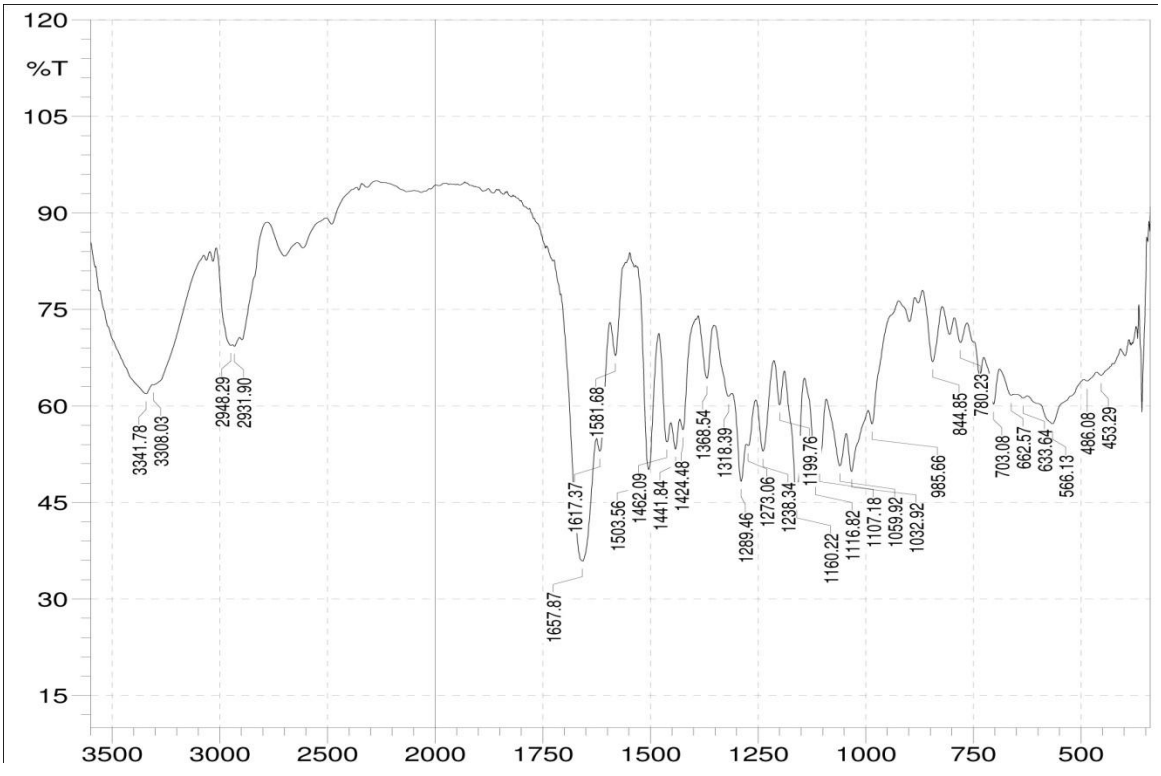


FIGURE 27 (m): FT-IR SPECTRUM OF (ORMELOXIFENE + SSG + CCS + MCC)

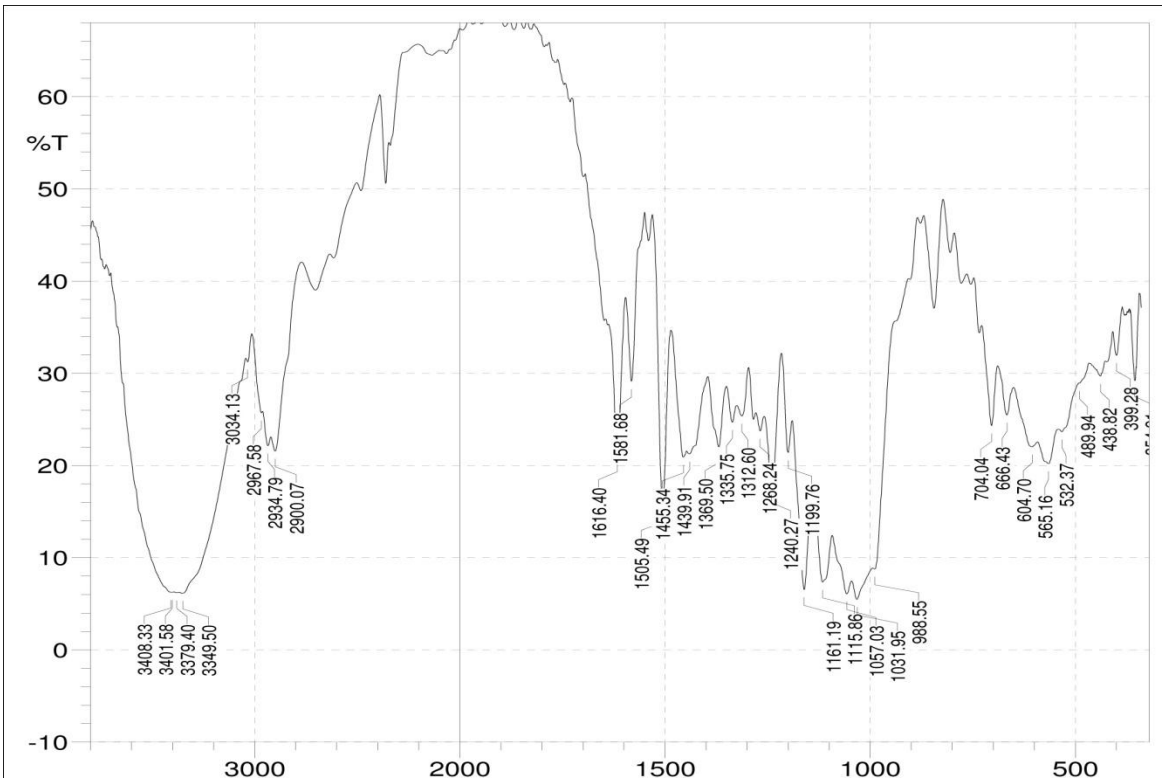


FIGURE 27 (n): FT-IR SPECTRUM OF (ORMELOXIFENE + BCD)

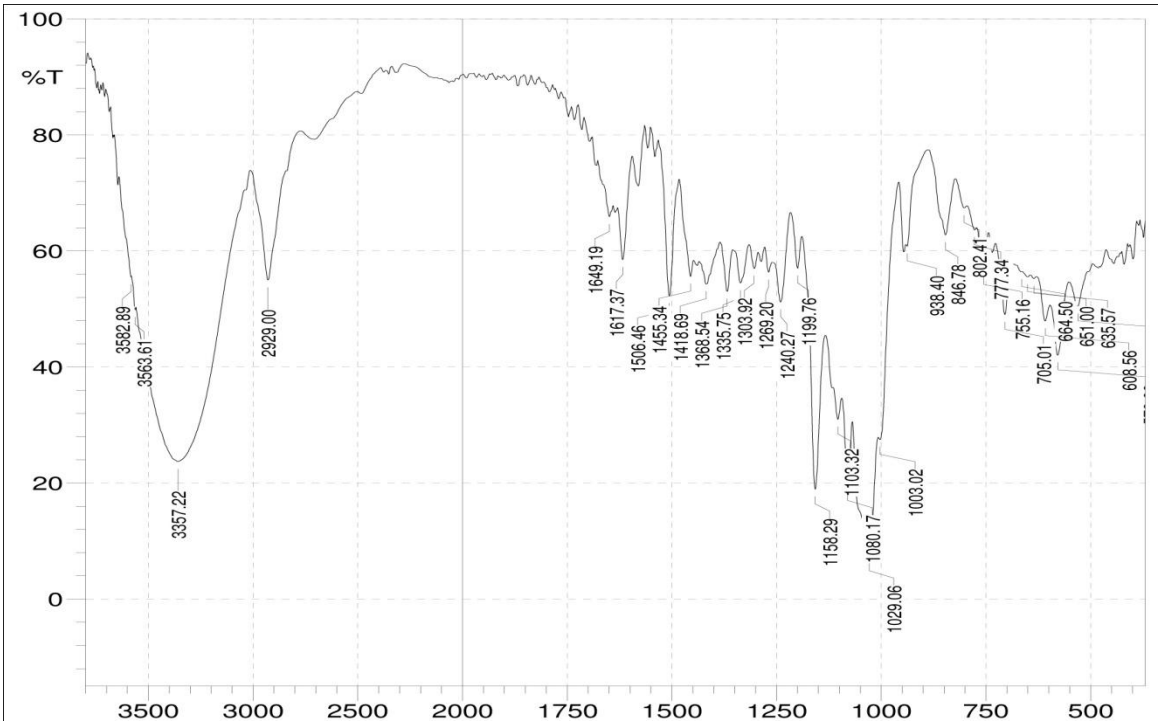


FIGURE 27 (o): FT-IR SPECTRUM OF (ORMELOXIFENE + CCS)

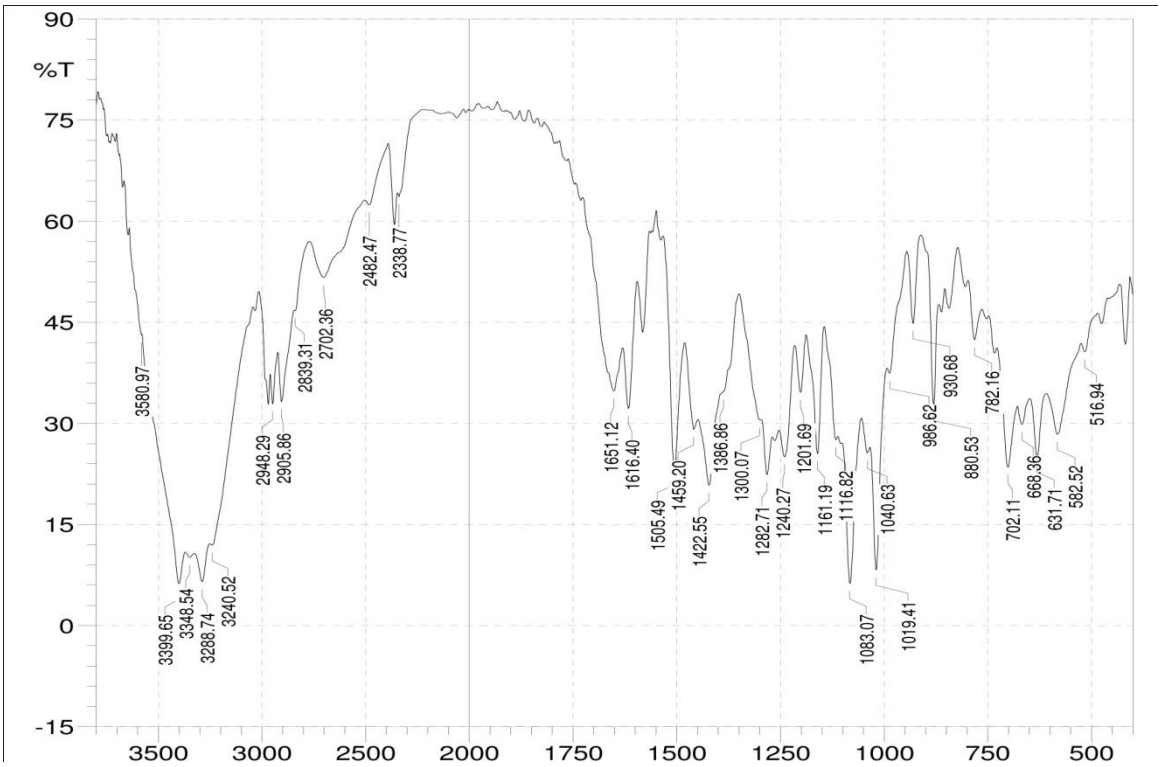


FIGURE 27 (p): FT-IR SPECTRUM OF (ORMELOXIFENE + CP)

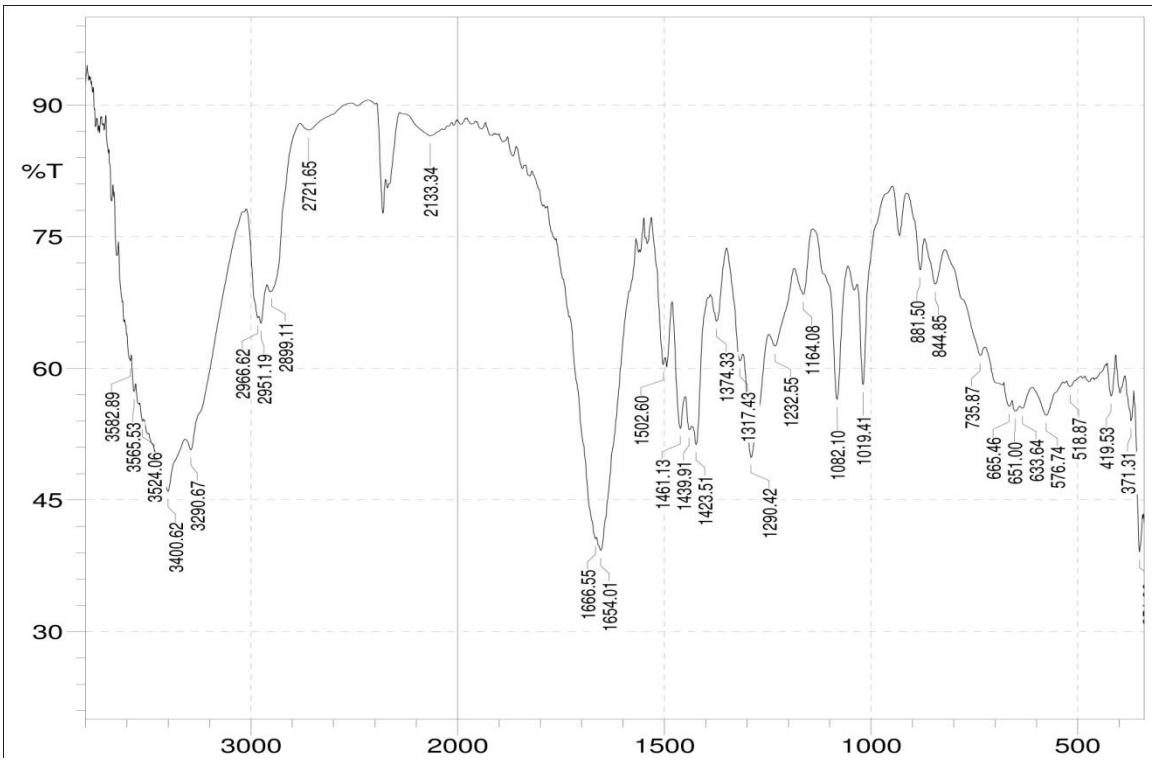


FIGURE 27 (q): FT-IR SPECTRUM OF (ORMELOXIFENE + PEG 6000)

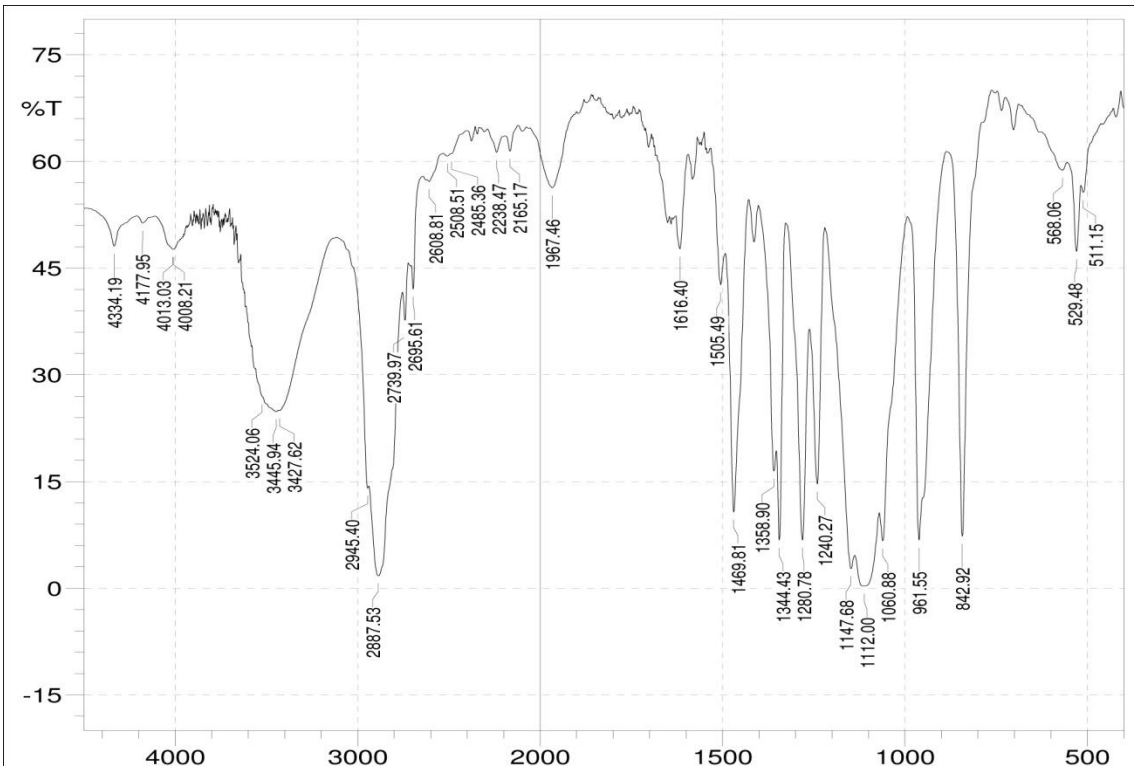


FIGURE 27 (r): FT-IR SPECTRUM OF (ORMELOXIFENE + SSG + CCS)

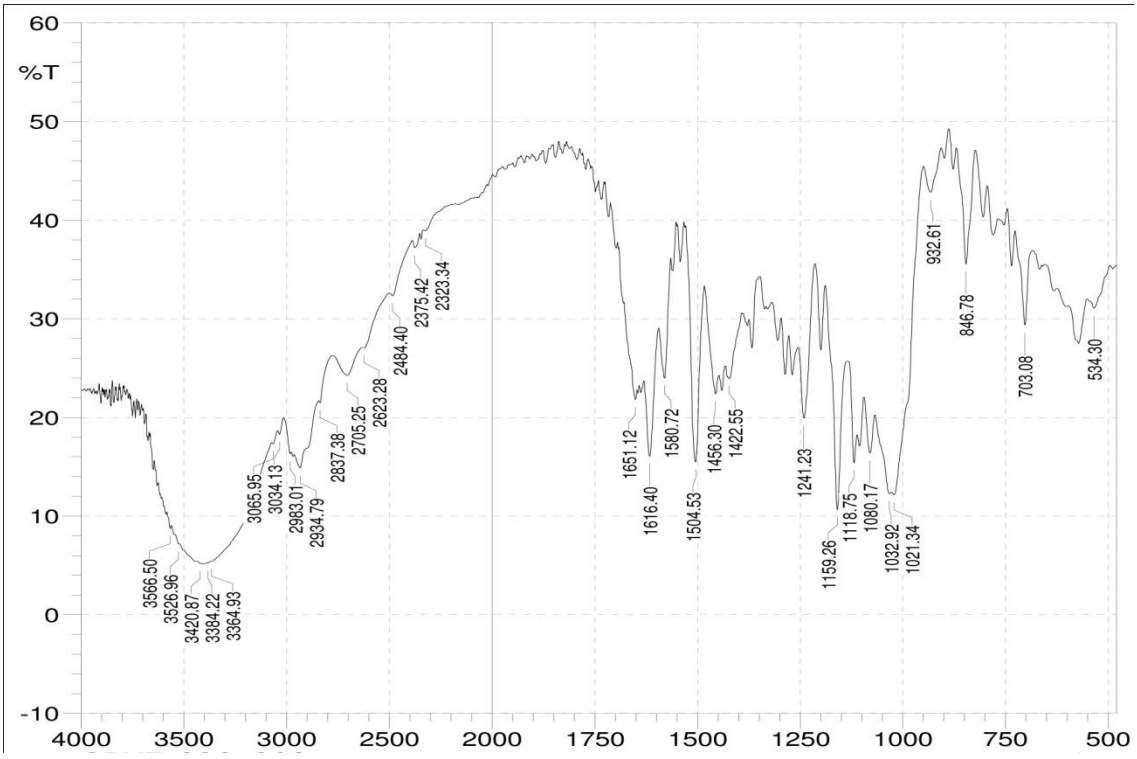


FIGURE 27 (s): FT-IR SPECTRUM OF (ORMELOXIFENE + SSG + MCC)

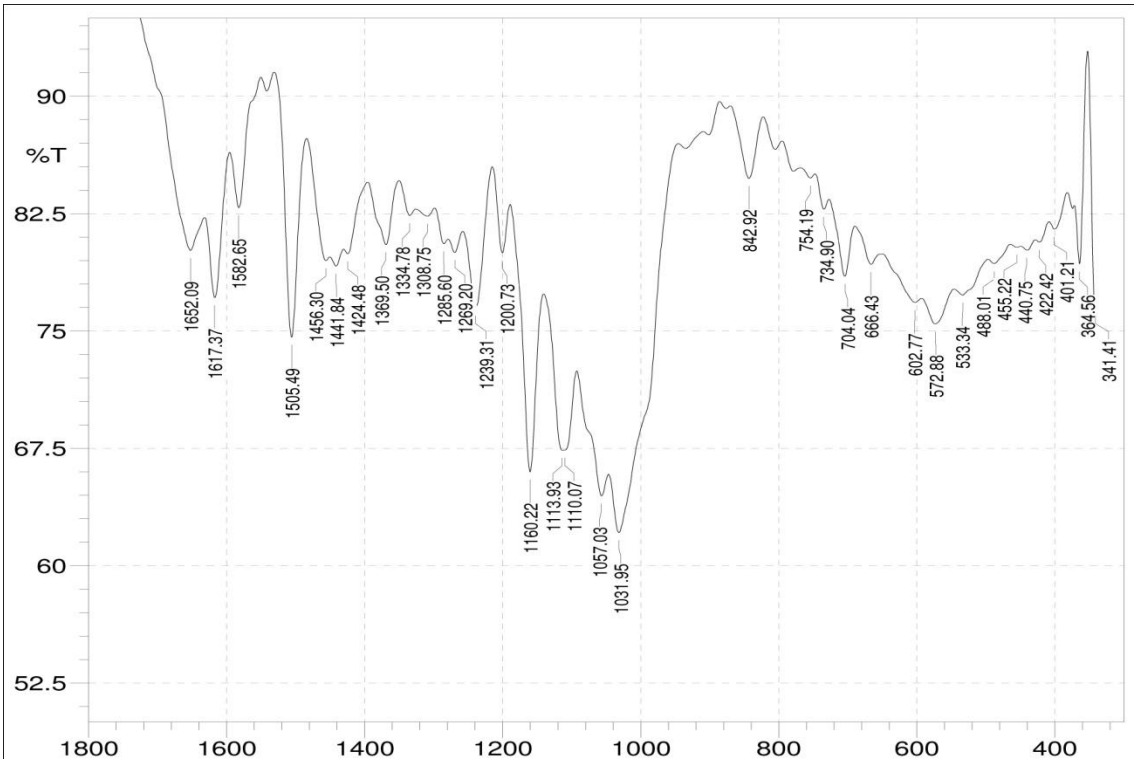


FIGURE 27 (t): FT-IR SPECTRUM OF (ORMELOXIFENE + SSG)

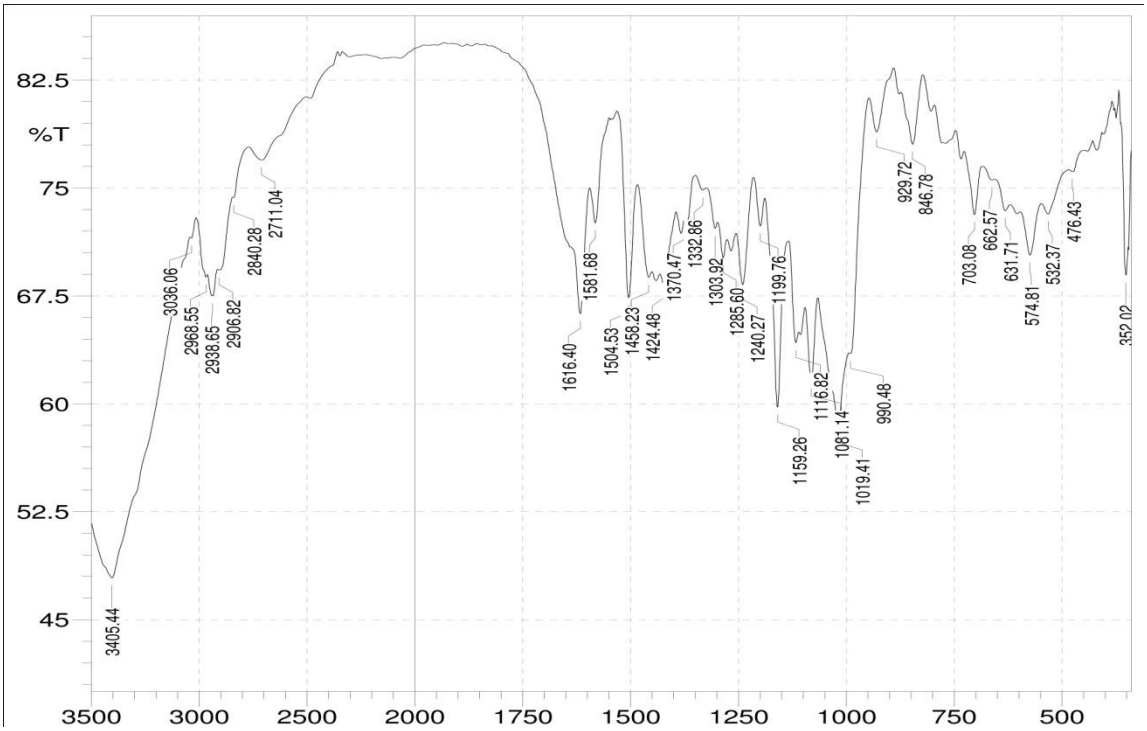


FIGURE 27 (u): FT-IR SPECTRUM OF KNEADING MIXTURE

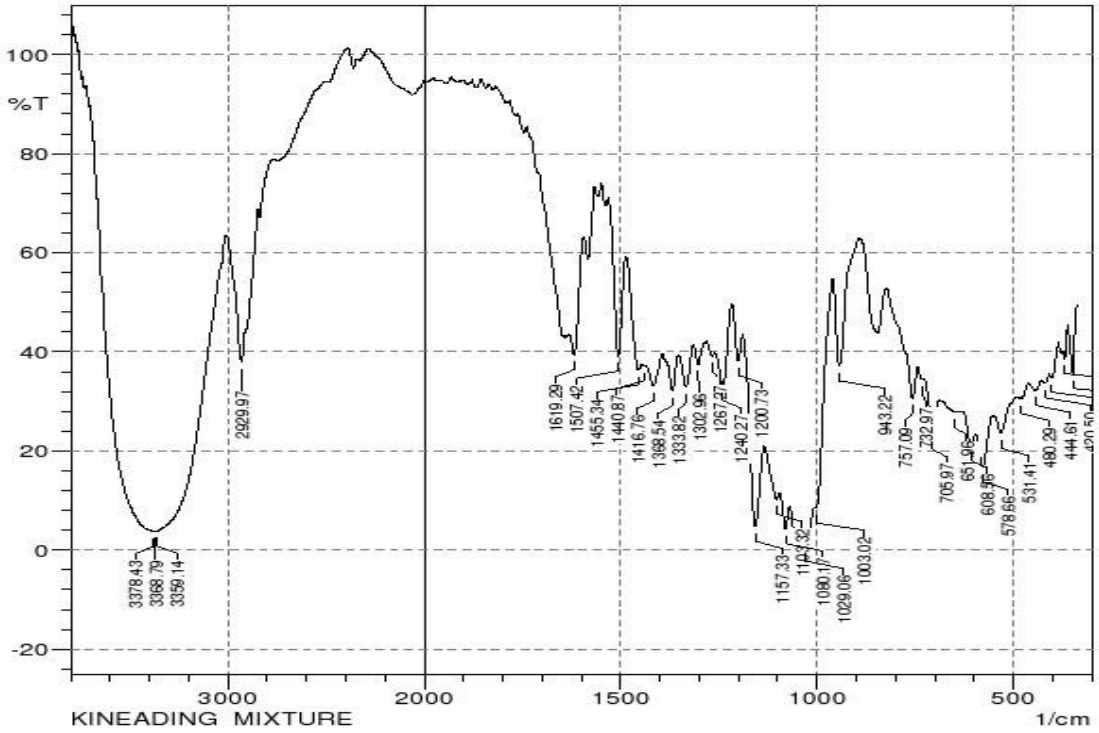


FIGURE 27 (v): FT-IR SPECTRUM OF FDT BEST FORMULATION (F8)

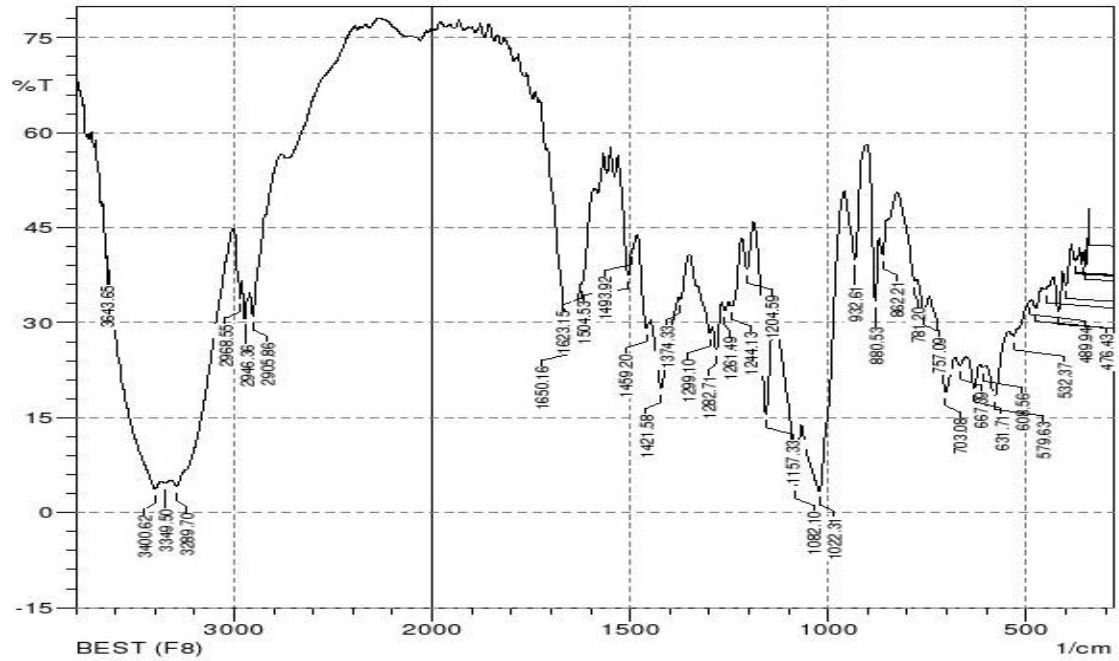


FIGURE 28 (a): DSC THERMODRAM OF ORMELOXIFENE

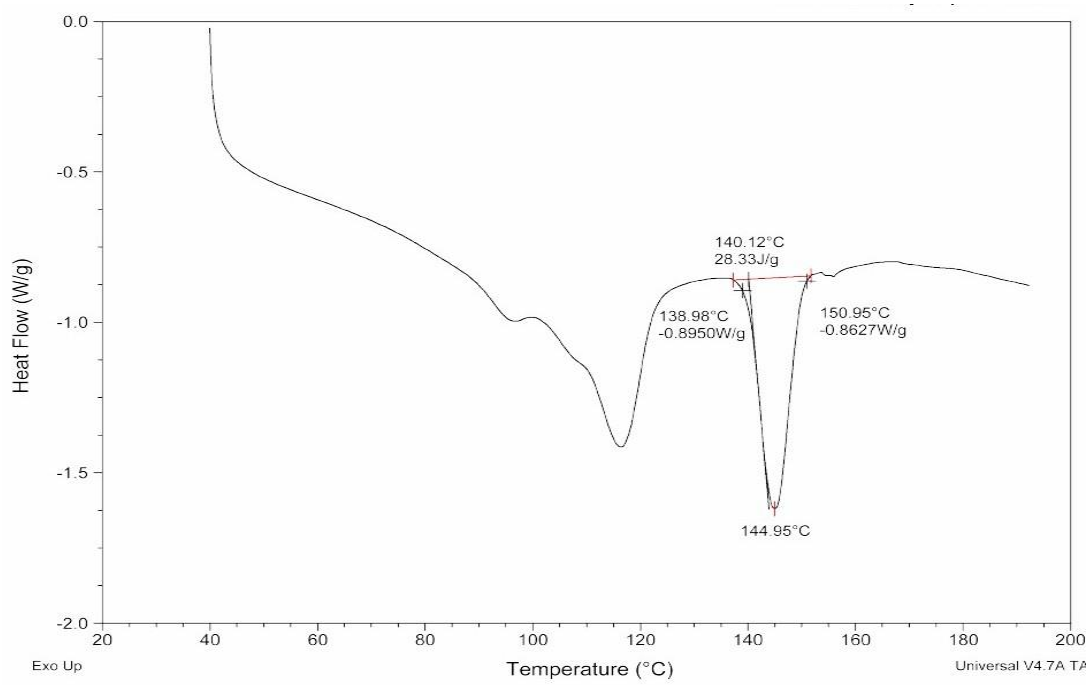


FIGURE 28 (b): DSC THERMODRAM OF BETACYCLODEXTRIN

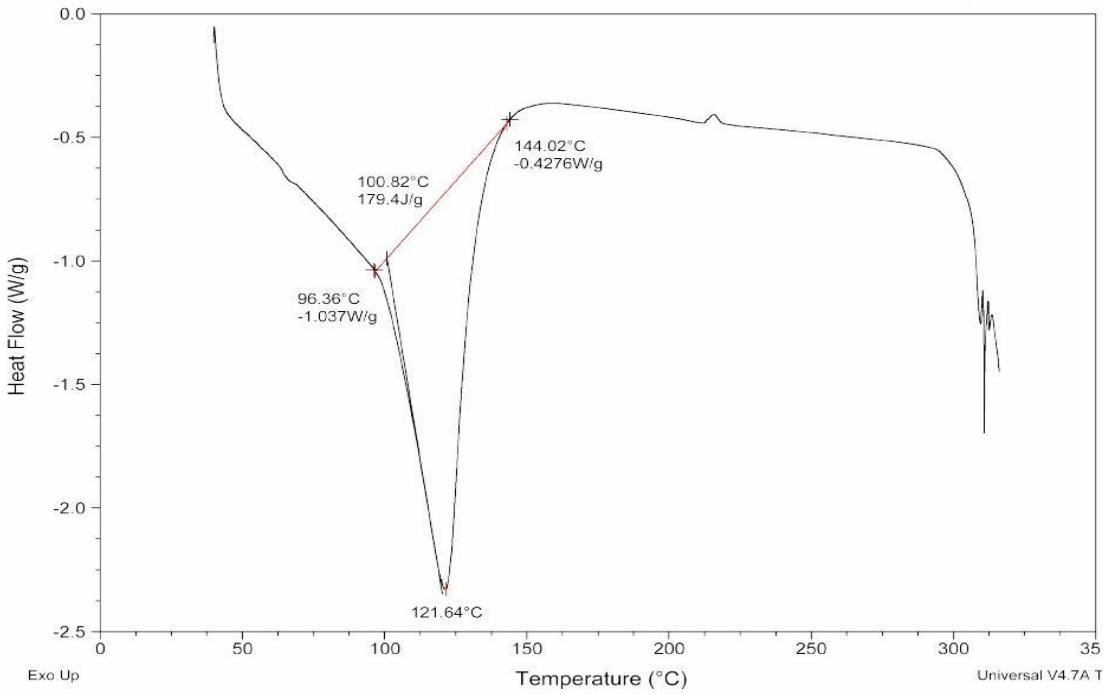


FIGURE 28 (c): DSC THERMODRAM OF PEG 6000

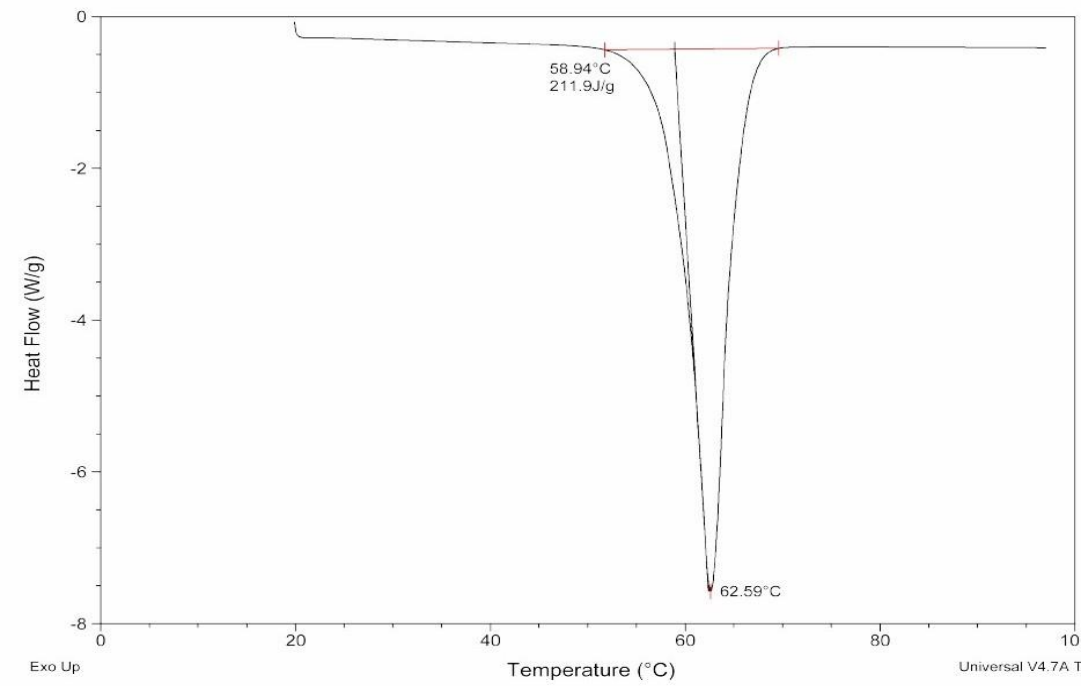


FIGURE 28 (d): DSC THERMODRAM OF CROSPOVIDONE

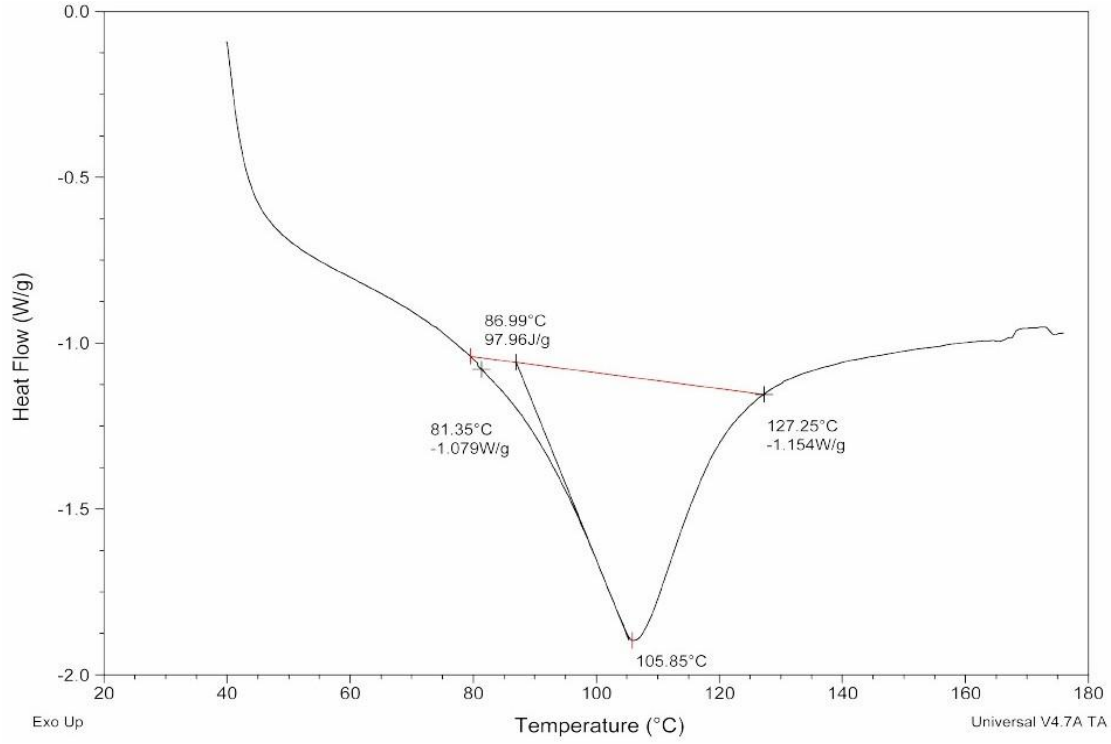


FIGURE 28 (e): DSC THERMOGRAM OF SODIUM STARCH GLYCOLATE

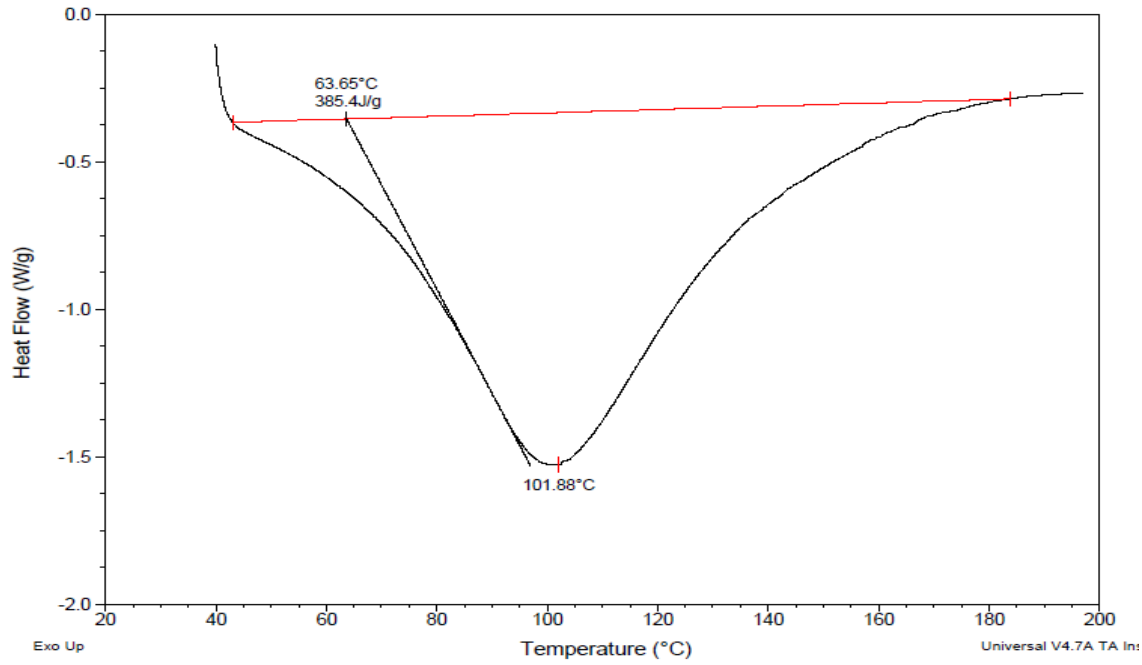


FIGURE 28 (f): DSC THERMOGRAM OF CROSCARMELLOSE SODIUM

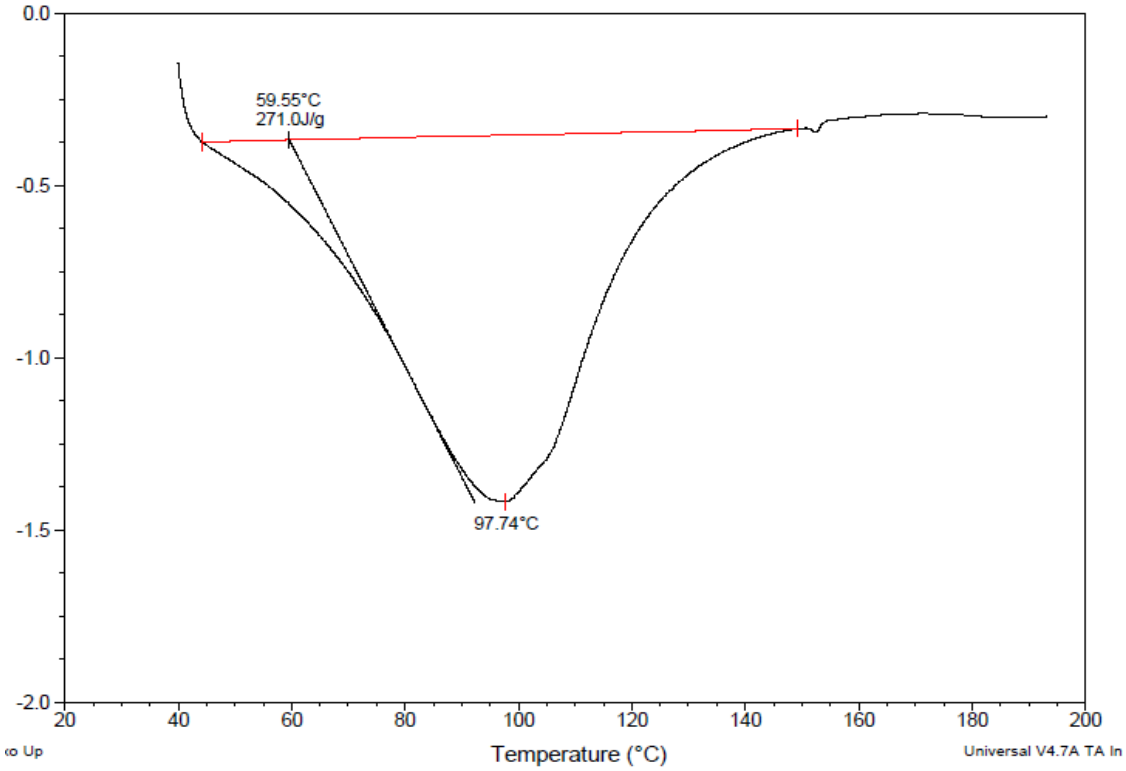


FIGURE 28 (g): DSC THERMODRAM OF MICROCRYSTALLINE CELLULOSE

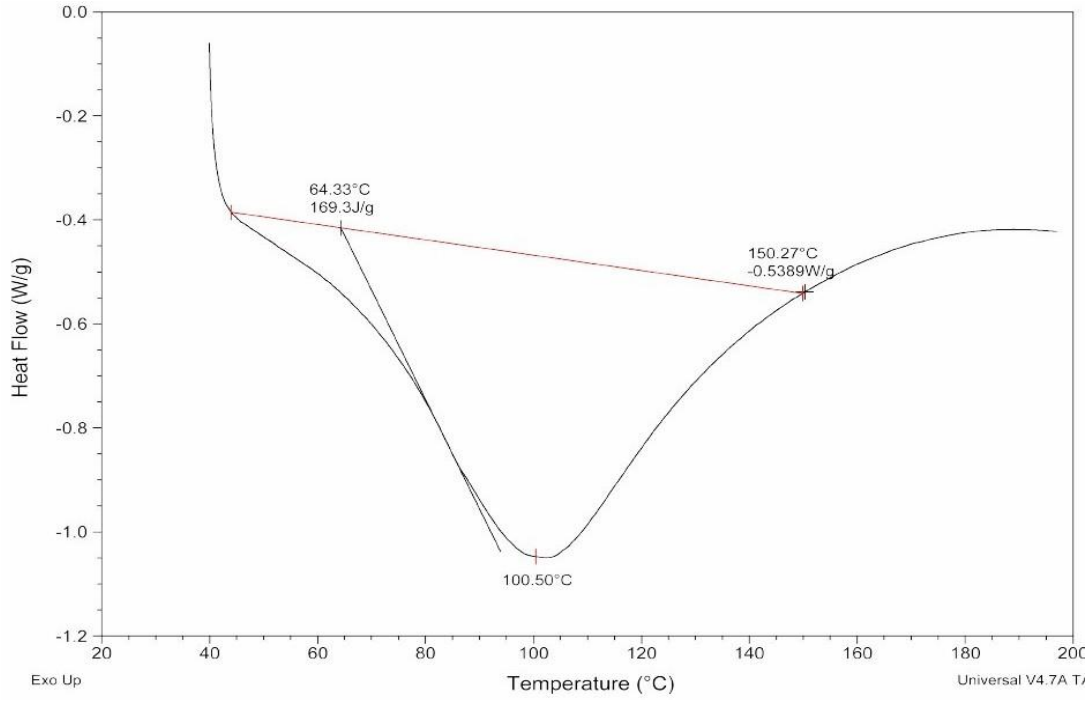


FIGURE 28 (h): DSC THERMODRAM OF PVP K30

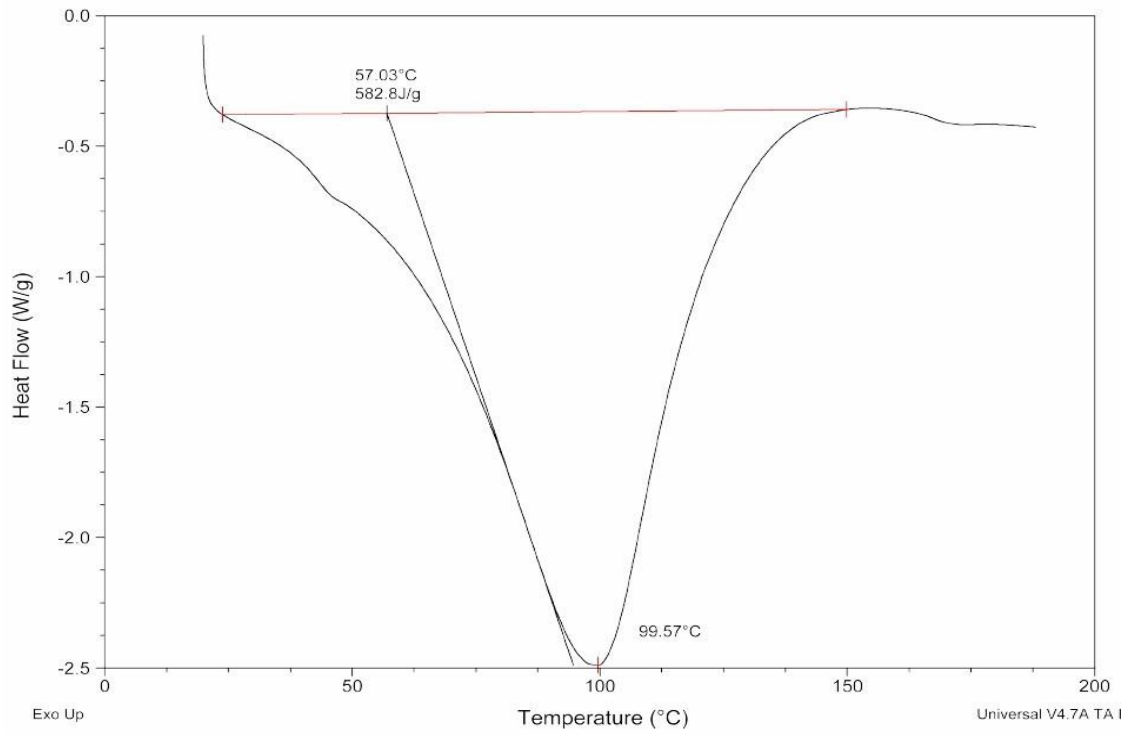


FIGURE 28 (i): DSC THERMODRAM OF KNEADING MIXTURE

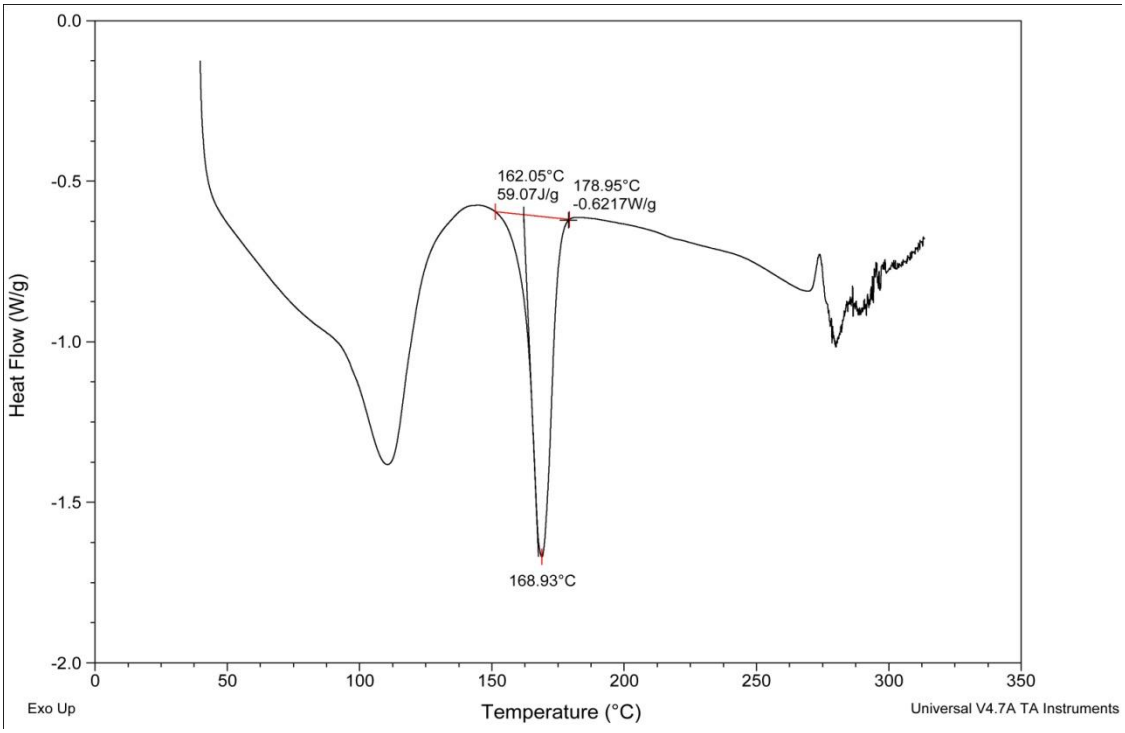


FIGURE 28 (j): DSC THERMODRAM OF FDT BEST FORMULATION (F8)

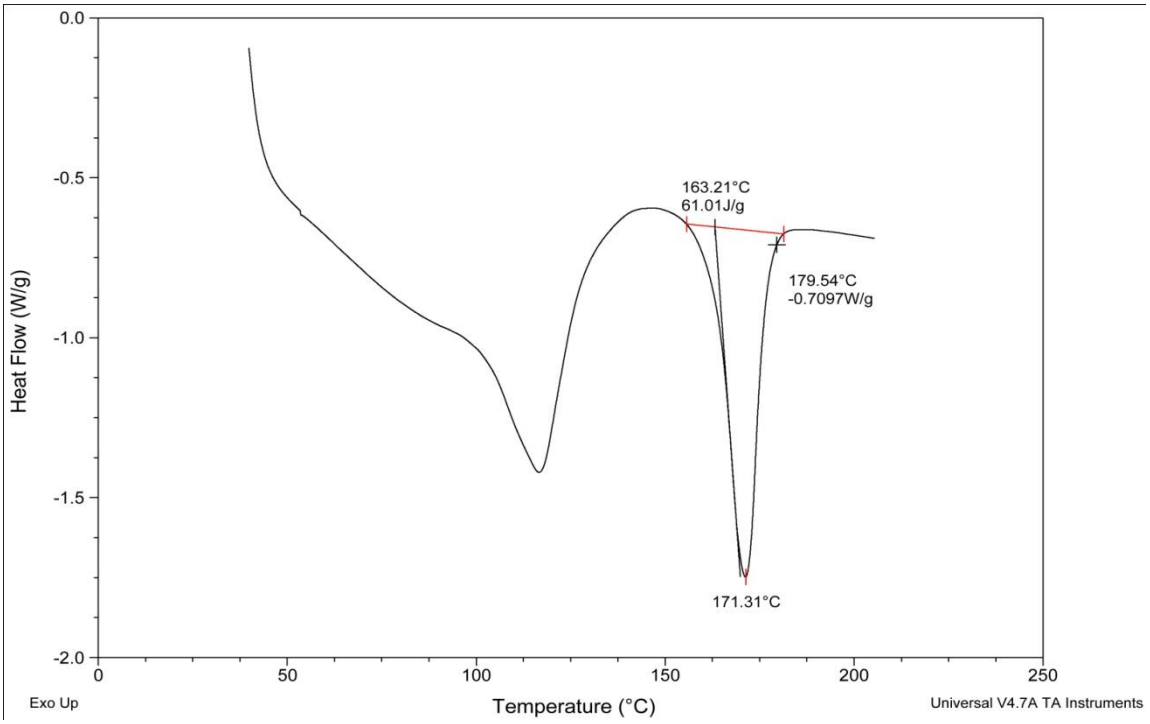


FIGURE 29 (a): XRD OF ORMELOXIFENE

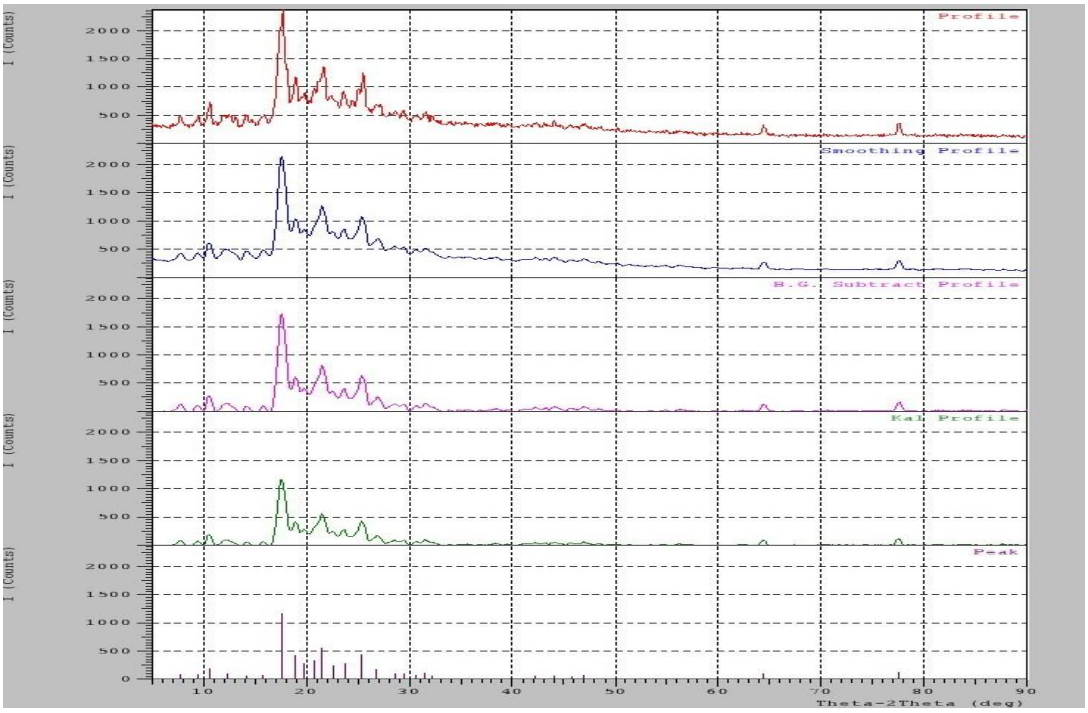


FIGURE 29 (b): XRD OF BETACYCLODEXTRIN

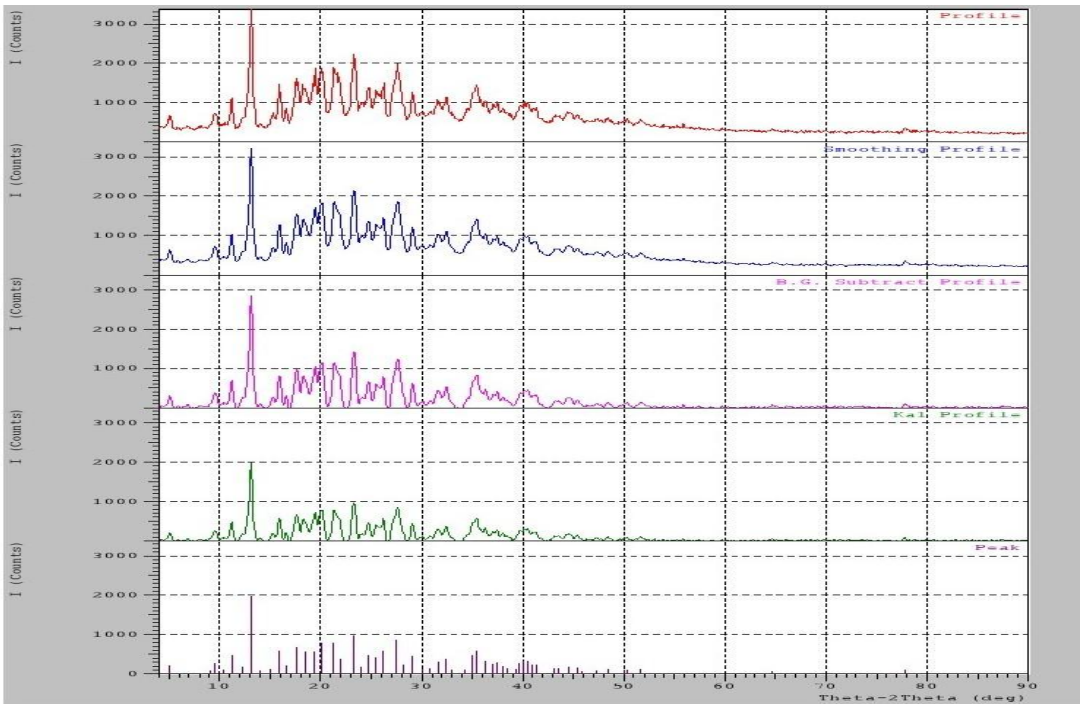


FIGURE 29 (c): XRD OF SODIUM STARCH GLYCOLATE

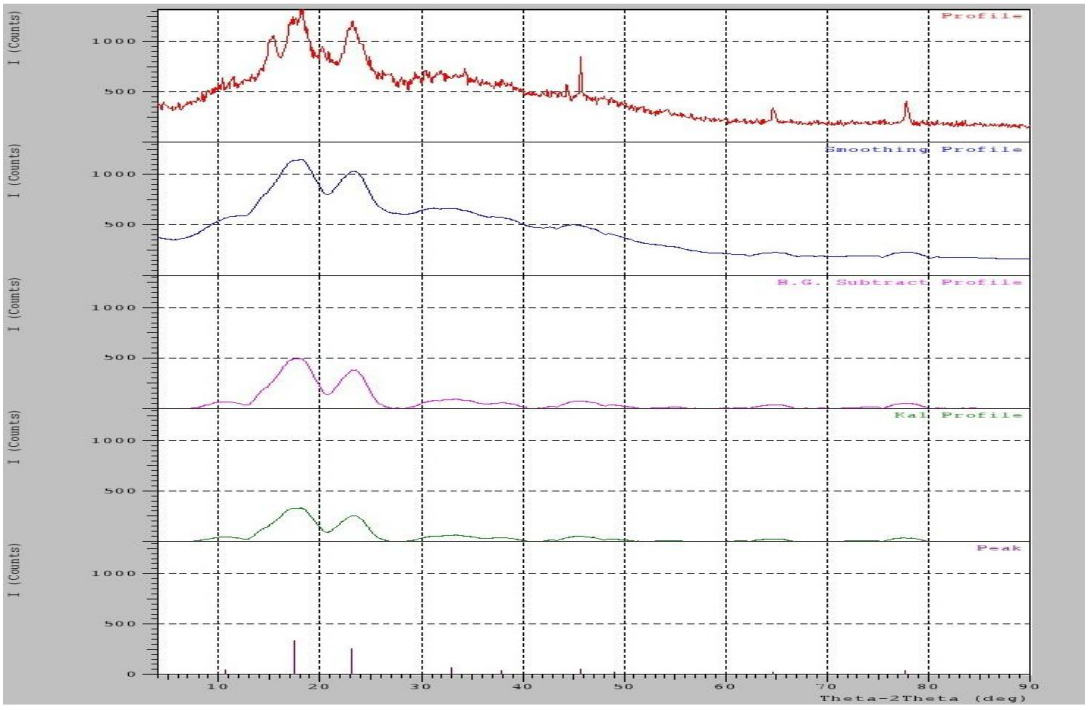


FIGURE 29 (d): XRD OF CROSPOVIDONE

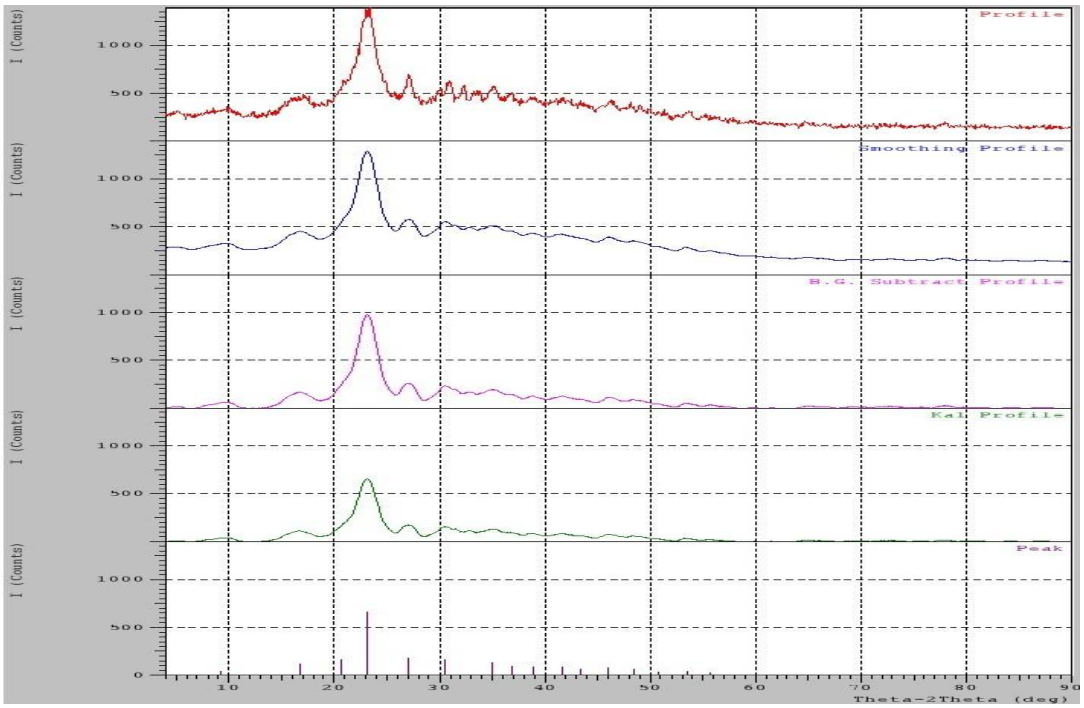


FIGURE 29 (e): XRD OF CROSCARMELLOSE SODIUM

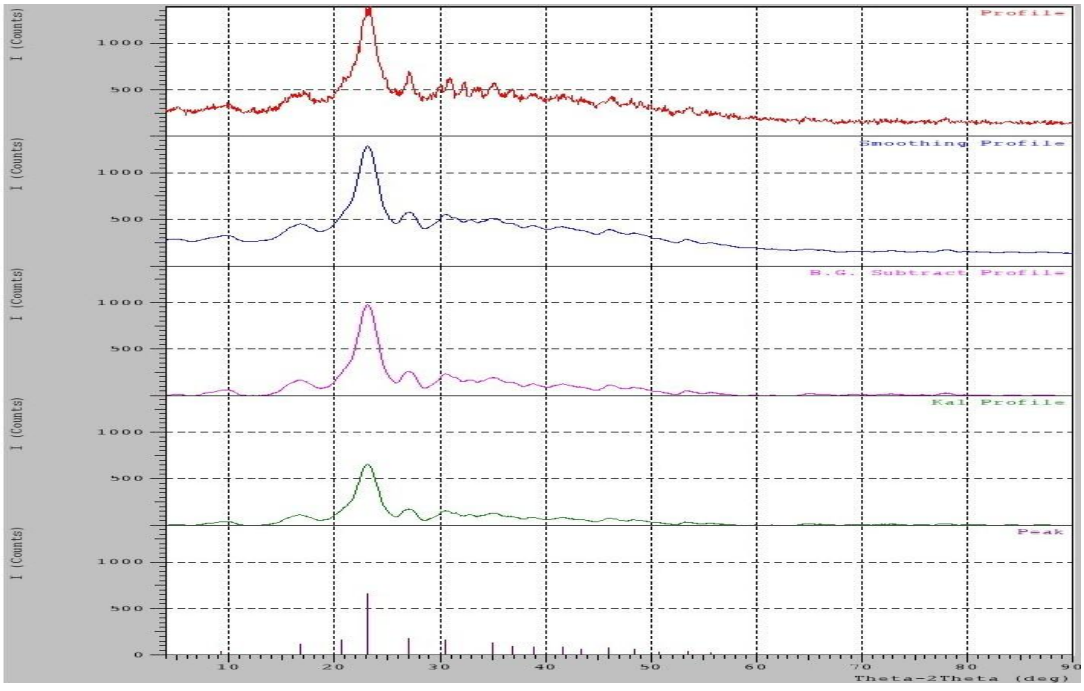


FIGURE 29 (f): XRD OF PVP K30

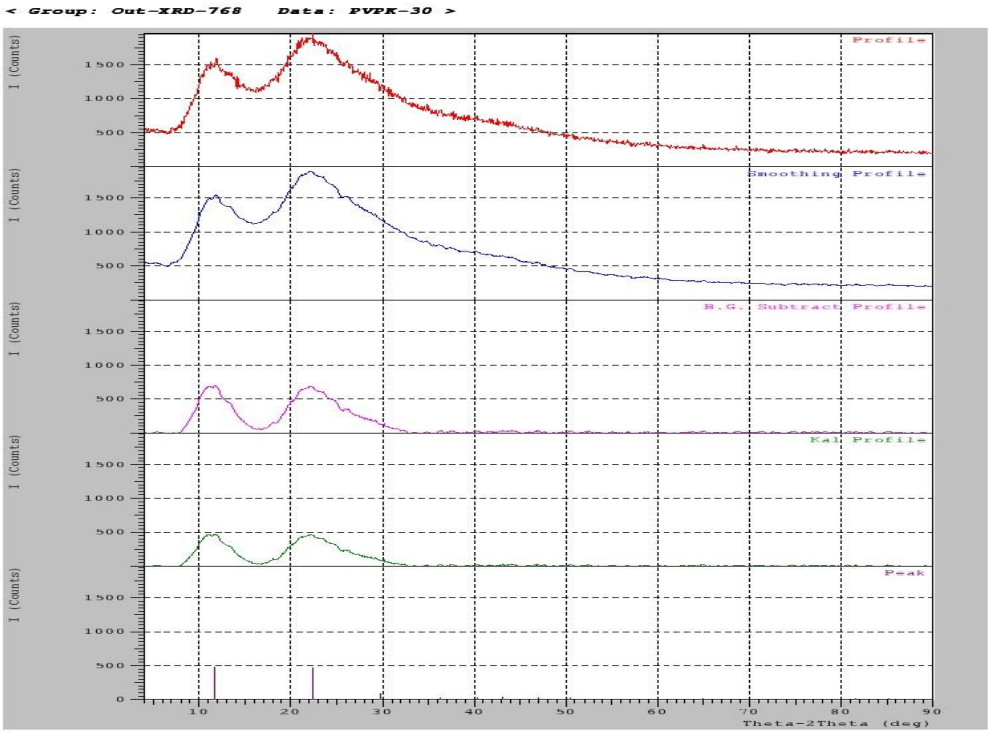


FIGURE 29 (g): XRD OF MICROCRYSTALLINE CELLULOSE

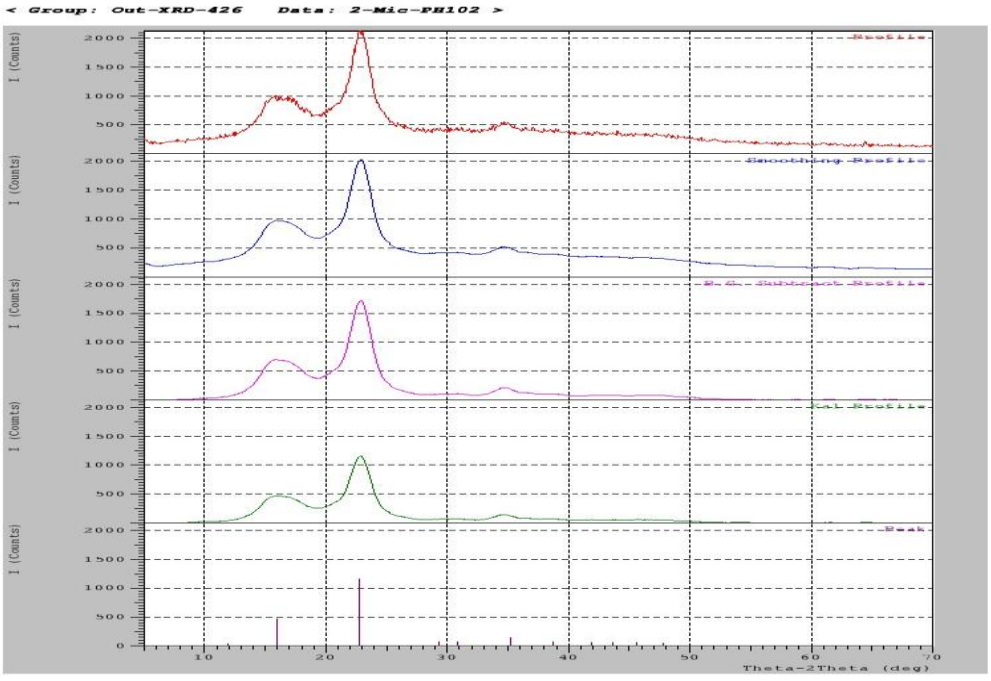


FIGURE 29 (h): XRD OF MANNITOL

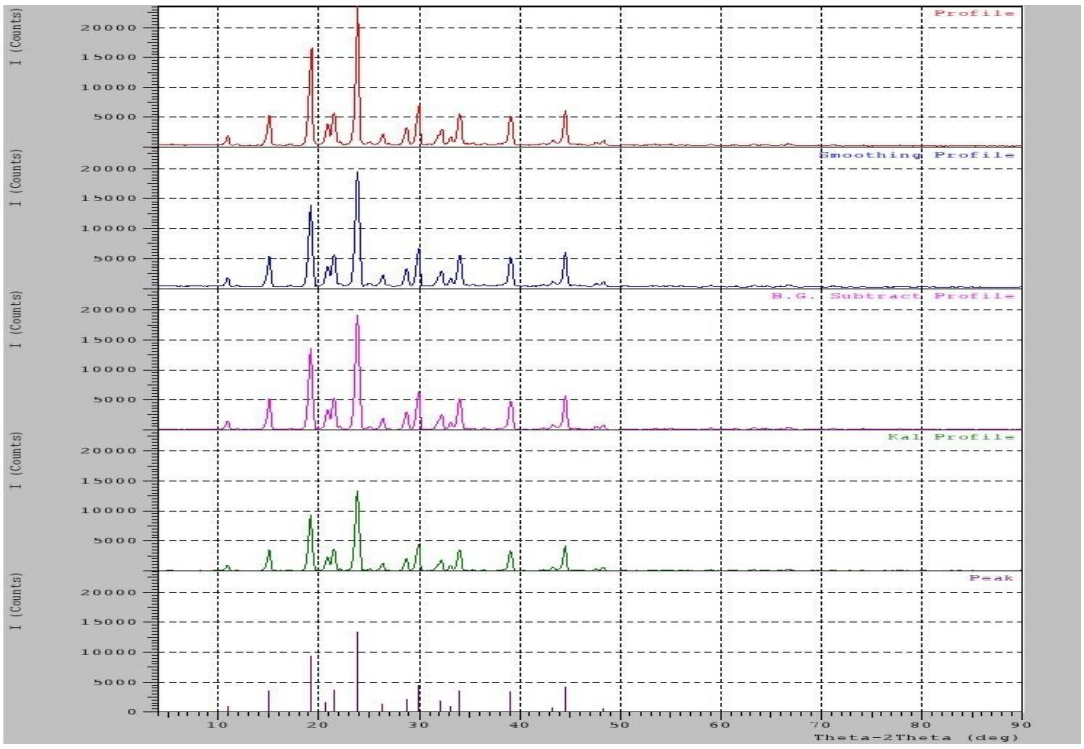


FIGURE 29 (i): XRD OF KNEADING MIXTURE

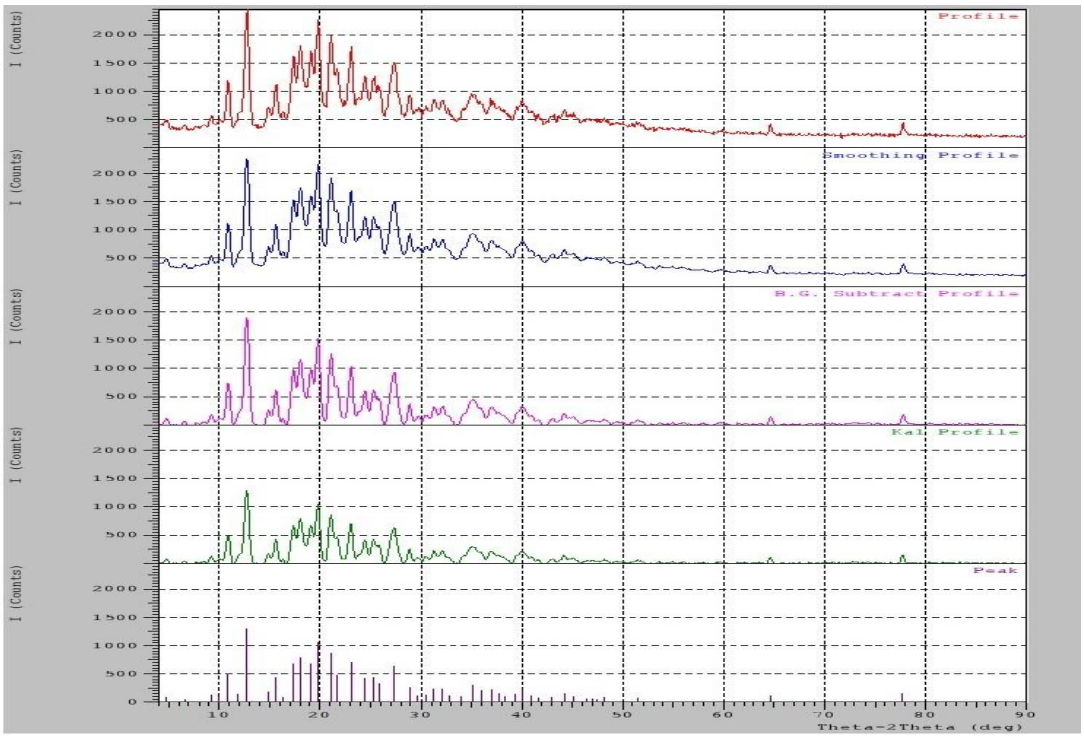
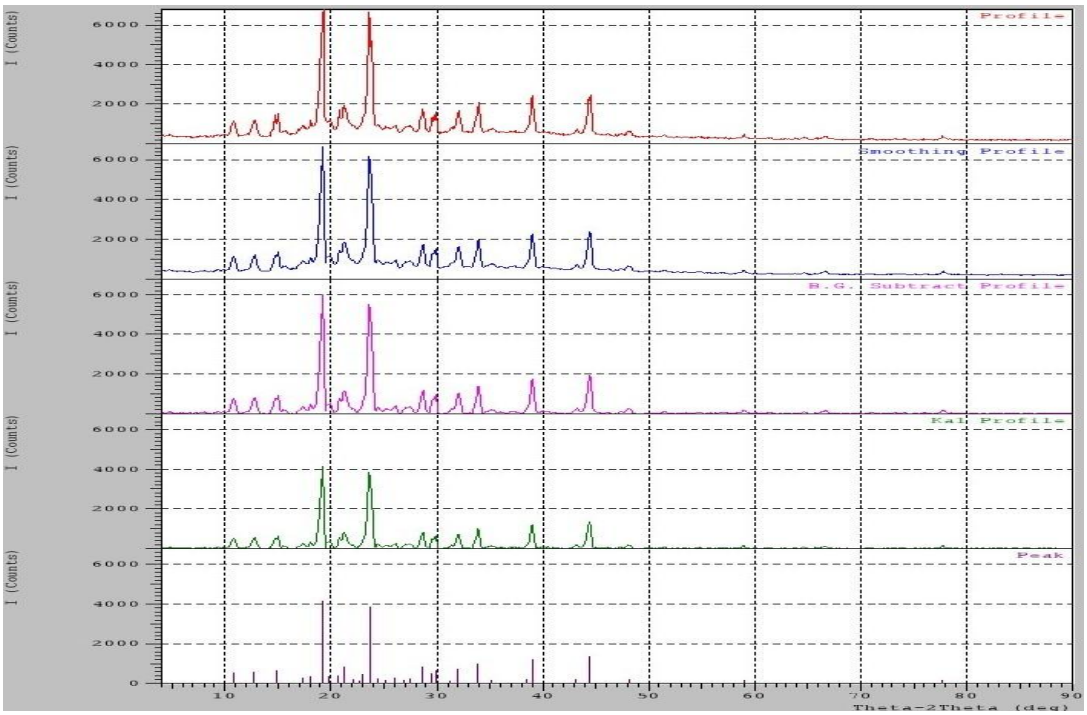


FIGURE 29 (j): XRD OF FDT BEST FORMULATION (F8)



CHAPTER XI

SUMMARY AND CONCLUSION

CHAPTER XI

SUMMARY AND CONCLUSION

- The purpose of this study was to prepare ormeloxifene fast dissolving tablets to improve the solubility and dissolution rate.
- Ormeloxifene is very slightly soluble in water; so the study was plan to done in two steps. The first step was to improve solubility of ormeloxifene by solid dispersion, second step was to formulate fast dissolving tablet by using first step resultant product.
- Kneading method, co precipitation, Melting Method and Solvent Evaporation Method were employed to prepare solid dispersions.
- The formulated solid dispersions were characterized for in vitro release studies in distilled water, using USP Type II apparatus.
- The solid dispersion systems of ormeloxifene hydrochloride prepared with the water soluble carriers betacyclodextrin and PEG 6000. Betacyclodextrin shows better *invitro* release.
- The results revealed that the increase in the carrier concentration decreases the dissolution rate (1:4 ratios).
- The invitro release studies revealed that the solid dispersion formulations showed a faster drug release when compared to the physical mixture and pure drug.
- Infrared spectroscopic studies showed that there is no interaction between the drug Ormeloxifene hydrochloride and the carriers.

- The results of the Powder X-ray diffraction studies proved that crystallinity of the drug Ormeloxifene hydrochloride was considerably reduced in the best formulation (K4).
- The solubility studies was observed that the solid dispersion (K- 4) have highest solubility compared to pure drug in distilled water and phosphate buffer pH 6.8.
- The DSC thermogram of ormeloxifene hydrochloride reveal that the sharp melting point peak appeared at 140.12^0C, whereas no such peak was observed in final product suggesting that Ormeloxifene hydrochloride was molecularly dispersed and in an amorphous form.
- The solid dispersion is stable under normal storage condition.
- The best resultant product was selected for fast dissolving formulation. The results of Differential Scanning calorimetry (DSC) and Fourier Transmission Infra-Red spectroscopy confirm that both drug (solid dispersion complex) and excipients are compatible with each other and are devoid of interactions.
- The results of precompression studies like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio reveals that the prepared powder blends of all formulations possess good flow properties.
- The tablets were prepared by direct compression method using superdisintegrants like Croscarmellose, Sodium starch glycolate, Crospovidone, Microcrystalline cellulose in different concentrations of 5%, 10 %, 15 %, PVP k-30 used as binder, and Mannitol is used as both sweetener and diluents, The tablets obtained were of uniform shape and size.
- The prepared tablets were subjected to post compression evaluations and the results indicate that

- The hardness, thickness and diameters of all the tablets are uniform, which ensures that all the tablets were of uniform size and shape with good resistance against mechanical damage.
- The tablets of all formulations contains uniform amount of drug, which ensures content uniformity for tablets of all formulations.
- The tablets were within the limits of weight variation test, which in turn indicate uniform distribution of contents of the powder blends of each formulations.
- The friability of all the tablets was found to be < 1%, which indicates the good mechanical resistance.
- The tablets of all formulations were found to have minimum wetting time and maximum water absorption ratio which is the desired characteristic of fast dissolving tablets, which enables faster disintegration of tablets.
- The disintegration time of all tablets were found to be less than three minutes, which ensures faster disintegration.
- The tablets of all the formulations were found to release more than 80% in 15 minutes, which is the desired quality of fast dissolving tablets that helps in faster absorption of the drug and quick onset of therapeutic effect except for formulations (F8). The dissolution pattern of various disintegrants used in the formulation was found to be in the order of combined super disintegrants Crospovidone > Croscarmellose sodium > Sodium starch glycolate.

CONCLUSION:

It was concluded, that ormeloxifene hydrochloride can be successfully formulated as fast dissolving tablets using various superdisintegrants in different concentrations by direct compression method.The formulation containing 5% of crospovidone, 5% croscarmellose sodium and 5% sodium starch glycolate as superdisintegrant was found to be outstanding than other formulations in terms of disintegration time and rate of dissolution.

REFERENCES

REFERENCES

Abdul Hasan Sathali A and Selvaraj V., 2012, "Enhancement of solubility and dissolution rate of Racecadotril by solid dispersion methods", *Jur. Curr. Chem. Pharm. Sc.: 2(3), 209-225*

Amit Modi, Vandana Singh, Arun Gupta, Ashlsh Agrawal , 2012, "Formulation and evaluation of Fast dissolving tablets of Diclofenac sodium using different superdisintigrants by direct compression method", *International journal of pharmaceutical & biological archives 3(4):1003-1007.*

Anas Bahnassi, Diana Zidan, , 2012, "Formulation & evaluation of Aceclofenac Fast dissolving tablets using foam granulation technique" , *Indo global journal of pharmaceutical sciences, 2(4): 342-347*

Anjan K Mahapatra, ,Narasimha Murthy P, Radha Rani E, Pallavi Soujanya S and Ruchita Kumari Patra.,2012, "An updated review on technically advances to enhance dissolution rate of hydrophobic drugs" , *Int. .Research journal of pharmacy 3(10).*

Anupama singh, Pramod Kumar Sharma, Jay Gopal Meher and Rishabha Malviya , 2011, "Evaluation of enhancement of solubility of Paracetamol by solid dispersion technique using different polymers concentration" , *Asian journal of pharmaceutical and clinical research Vol. 4.*

AppaRao. B*, M. R. Shivalingam, Y. V. Kishore Reddy, Somesekhara Rao, Rajesh. K,N. Sunitha ,2010, "Formulation and evaluation of Aceclofenac solid dispersions for dissolution rate enhancement", *International journal of pharmaceutical sciences and drug research 146-150.*

ArunPrasad*, N. Narayanan, G. Rajalakshmi, 2010, "Preparation and evaluation of solid dispersion of Terbinafine hydrochloride", *International journal of pharmaceutical sciences review and research.*

Ashish Garg, and Gupta M. M ,, 2012, "Mouth dissolving tablets- a review", *Journal of drug delivery & therapeutics, 3(2), 207-214.*

Ashish.P, Harsoliya MS, Pathan J K and Shruti S , 2011, "A review- formulation of Mouth dissolving tablet", *Int. Jur. of pharmaceutical and clinical science*.

Chaudhary V.B and Pate J.K., 2012, "Cyclodextrin inclusion complex to enhance solubility of poorly water soluble drugs*", ijpsr, 2013; vol. 4(1): 68-76.*

Claudia yanezet, Paulina Canete-Rosales, Juan Pablo Castillo, Nicole Catalan, and Tomas Undabeytia , 2012, "Cyclodextrin inclusion complex to improve physicochemical properties of herbicide Bentazon exploring better formulations", *Plos one , www.plosone.org 1 volume 7 , issue 8 ,e41072.*

Daisy Sharma, Mohit Soni, Sandeep Kumar and GD Gupta, 2009, "Solubility enhancement – eminent role in poorly soluble drugs", *Research j. Pharm. And tech.2.*

Dali Shukla, Subhashis Chakraborty, Sanjay Singh, Brahmeshwar Mishra *., 2009 , "Mouth dissolving tablets - An overview of evaluation techniques", *Sci pharmaceutica*.

Debjit Bhowmik*, Chiranjib.B, Krishnakanth, Pankaj, R.Margret Chandira, 2009, "Fast dissolving tablet: an overview", *Journal of chemical and pharmaceutical research,163-177.*

Deepthi mathew., 2009, "A study on suitability of Nimesulide-betacyclodextrin complex in oral and topical dosage forms", *International journal of pharmacy and pharmaceutical sciences, vol. 1, suppl 1.*

Devandra Revanal Rane, Hemant Narhar Gulve, Vikas Vasant Patil, Vinod Madhaorao Thakare and Vijay Raghunath Patil , 2012, "Formulation and evaluation of Fast dissolving tablet of Albendazole", *International current pharmaceutical journal, 1(10): 311-316.*

Dhaval Shah and Sudarshan Singh , 2012, "Development and characterization of Mouth dissolving tablet of Zolmitriptan" *Asian pacific journal of tropical disease (2012)s457-s464.*

Ehsan Ali Mohamed, Dr. Shaimaa N. Abd Al Hammid, 2013, "Formulation and evaluation of Rosuvastatin Orodispersible tablets", *International journal of pharmacy and pharmaceutical sciences vol 5, suppl 2.*

Hyma .P, Ravikanth.N, and Pradeep Reddy C.H, 2012 , "Improvement of solubility and dissolution rate of Pioglitazone by solid dispersions technique", *International journal of advances in pharmaceutical sciences volume 3 issue 6 pages 423-431.*

Imran Shekh, Vishal Gupta, Abhay Jain and Naveen Gupta, 2011, "Preparation and characterisation of beta cyclodextrin Aspirin Inclusion complex", *International journal of pharmacy & life sciences.*

Indian Pharmacopiea, 2010.

Jagadevappa Patil, Shivand Shiralasetti and Ajaykumar Patil , 2010, "Influence of method of preparation on solubility, physicochemical properties and in-vitro release

profile of Simvastatin- cyclodextrin inclusion complexes- a comparative study", *international journal of chemtech research, vol.2, no.1, pp 562-571.*

Jain C Pand Naruka PS, 2009, "Formulation and evaluation of fast dissolving tablets of Valsartan", *International journal of pharmacy and pharmaceutical sciences, vol. 1.*

Jeevana jyothi.B and suneela ., 2010, "Development of fast dissolving tablets of Glibenclamide using crospovidone and its kneading mixture",*Indian j.pharm. Educ. Res. 44(4).*

Kamal dua, Ramana MV, Singh Sara UV, Himaja M, Abhinav Agarawal, Vaibhav Garg and Kavita Pabreja.,2007, "Investigation of enhancement of solubility of Norfloxacin beta-cyclodextrin in presence of acidic solubilizing additives", *Current drug delivery 4, 21-25.*

Karthikeyan M, Umarul Mukhthar AK, Megha M, Shadeer Hamza P, 2012, "Formulation of Diclofenac tablets for rapid pain relief", *Asian pacific journal of tropical biomedicine 308-311.*

Kothawade S. N.*, Kadam N. R., Aragade P. D., Baheti D. G, 2010, "Formulation and characterization of Telmisatan solid dispersions", *International journal of pharmtech research: ijprif, vol.2, no.1, pp 341-347.*

Mohan Kumar.V, Manjula.BP, 2013, "Formulation and evaluation of Rosuvastatin Orodispersible tablets", *Ujp page no 26-37.*

Mohamed Gulzar Ahmed, Kirankumar GB, Satishkumar BP and Harish AR, 2010, "Formulation and evaluation of solid dispersion of Aceclofenac ", *An international journal of advances in pharmaceutical sciences vol.1.*

Nagendra Rao R, Suchetha Reddy Aleti, Rengaraju D, Aman kant, Shankraiah MM, Venkatesh JS and C.nagesh, 2011, "Solubility and dissolution enhancement of Cefixime using natural polymer by solid dispersion technique", *International journal of research in pharmacy and chemistry.*

Narmada GY, Mohini K, Prakash Rao B, Gowrinath DXP, Kumar KS, 2009, "Formulation, evaluation and optimization of Fast dissolving tablets containing Amlodipine besylate by sublimation method", *Ars pharm, vol. 50, 129-144.*

Payal H. Patil, Veena S. Belgamwar, Pratibha R. Patil, and Sanjay J. Surana., 2013, "Solubility enhancement of Raloxifene using inclusion complexes", *Hindawi publishing corporation journal of pharmaceutics volume, article id 527380, 9 pages.*

Prabhakar Shires, Sreenivasa Rao.K and Mohamed Majid Iqbal , 2012, "Formulation and evaluation of cyclodextrin inclusion complex tablets of water insoluble drug-Glimipiride", *International journal of research in pharmacy and chemistry.*

Prasanth.VV, Abhilash M, Shanth kumar, Rinku Mathappan, Sourav Tribedi and Sam T Mathew, 2013, "Formulation and evaluation of solid dispersion of Melitracen*", International journal of pharmaceutical and chemical sciences,*

Ravi S Wanare and Ravikant S Murkute., 2012, "Formulation and evaluation of Fast dissolving tablets of Azithromycin dihydrate using different super disintegrants", *Pharmacie globale (ijcp) 2012, 4 (05).*

Saravanakumar K ,Nagaveni P, Chandra sekar K B, Jayachandra Reddy P and Grace Rathnam, 2011, "Fast dissolving tablet background, trends and perspectives- a review", *Int.Jur..rev.life.sci, 1(3) page 88-90.*

Sawarikar P.P, Sridhar B K, and Shivkumar S, 2010, "Formulation and evaluation of fast dissolving / disintegrating tablets of Isoxsuprine hydrochloride", *Journal of current pharmaceutical research; 3(1): 41-46.*

Seitia Anupama, Goyal Surinder, Shrivastva Birendra and Goyal N , 2011, "Design, optimization, preparation and evaluation of solid dispersions of Albendazole using factorial design", *Pelagia research library der pharmacia sinica, 2 (5):30-42*

Shobhitkumar Sstish kumar Gupta, and promod Kumar Sharma, 2011,"Dissolution rate enhancement of Aceclofenac by solid dispersion technique", *Asian journal of pharmacy and life science vol. 1(4)*

Shukla Vikesh*, Masareddy Rajashree, Anghore Ashok, Manvi Fakkirappa.V., 2009, "Influence of ß-cyclodextrin complexation on ketoprofen release from matrix formulation", *International journal of pharmaceutical sciences and drug research, 1(3): 195-202.*

Suhas M. Kakade*, Vinodh S. Mannur, Ketan B. Ramani, Ayaz A. Dhada, Chirag V. Naval, Avinash Bhagwat., 2010, "Formulation and evaluation of mouth dissolving tablets of Losartan potassium by direct compression techniques", *Int. J. Res. Pharm. Sci. Vol-1, 290-295.*

Thakur Anil Kumar, Nirmala, Harikumar, 2013, "Various techniques enhancing bioavailabilty of poorly water soluble drugs", *Journal of drug delivery & therapeutics; 2013, 3(2), 215-221.*

Tomar V , Garud N, Kannojia P, Garud A, Jain N K, and Singh N, 2010," Enhancement of solubility of Acyclovir by solid dispersion and inclusion complexation methods" , *scholars research library Der pharmacia lettre, 2(5): 341-352*

Vineet Bhardwaj, Mayank Bansal and P.K. Sharma, 2010, "Formulation and evaluation of Fast dissolving tablets of Amlodipine besylate using different super disintegrants and camphor as sublimating agent", *American-eurasian journal of scientific research 5 (4): 264-269.*

Yogesh S thorat Indrajeet D.Gonjari and Avinash H.Hosmani , 2011, "Solubility enhancement techniques: a review on conventional and novel approaches*", Ijpsr, vol. 2(10): 2501-2513*